

PENT COOPERATION TREA

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NOTIFICATION OF ELECTION  
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 October 2000 (12.10.00)	Assistant Commissioner for Patents United States Patent and Trademark Office Box PCT Washington, D.C.20231 ETATS-UNIS D'AMERIQUE
International application No. PCT/AU00/00103	Applicant's or agent's file reference 7464594/RMH
International filing date (day/month/year) 15 February 2000 (15.02.00)	Priority date (day/month/year) 15 February 1999 (15.02.99)
Applicant HEATON, Andrew et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

13 September 2000 (13.09.00)

in a notice effecting later election filed with the International Bureau on:

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Manu Berrod
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 26 JUN 2001

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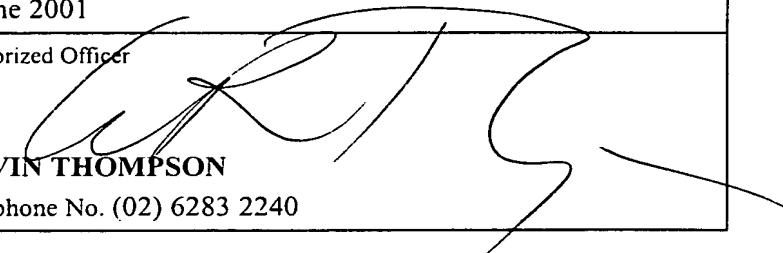
Applicant's or agent's file reference 7464594/RMH	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. <b>PCT/AU00/00103</b>	International Filing Date ( <i>day/month/year</i> ) 15 February 2000	Priority Date ( <i>day/month/year</i> ) 15 February 1999
International Patent Classification (IPC) or national classification and IPC <b>Int. Cl.</b> <sup>7</sup> C07D 311/36, 311/38, 311/04, 311/56		
Applicant NOVOGEN RESEARCH PTY LTD et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.  
 This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 5 sheet(s).

3. This report contains indications relating to the following items:

- |      |   |
|------|---|
| I    | <input checked="" type="checkbox"/> Basis of the report   |
| II   | <input type="checkbox"/> Priority   |
| III  | <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability   |
| IV   | <input type="checkbox"/> Lack of unity of invention   |
| V    | <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| VI   | <input type="checkbox"/> Certain documents cited  |
| VII  | <input type="checkbox"/> Certain defects in the international application   |
| VIII | <input type="checkbox"/> Certain observations on the international application  |

Date of submission of the demand 13 September 2000	Date of completion of the report 5 June 2001
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer  <b>GAVIN THOMPSON</b> Telephone No. (02) 6283 2240

**I. Basis of the report**

1. With regard to the elements of the international application:\*

- the international application as originally filed.
- the description,      pages **1 to 38** as originally filed,  
                        pages , filed with the demand,  
                        pages , received on with the letter of  
 the claims,      pages **39 to 45** as originally filed,  
                        pages , as amended (together with any statement) under Article 19,  
                        pages , filed with the demand,  
                        pages **46 to 50** received on **4 May 2001** with the fax of **4 May 2001**
- the drawings,      pages , as originally filed,  
                        pages , filed with the demand,  
                        pages , received on with the letter of
- the sequence listing part of the description:  
                        pages , as originally filed  
                        pages , filed with the demand  
                        pages , received on with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language which is:

- the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, was on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4.  The amendments have resulted in the cancellation of:

- the description,      pages
- the claims,          Nos.
- the drawings,        sheets/fig.

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\*

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\* Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Claims 9 to 26, 31 to 39, 44 to 46	YES
	Claims 1 to 8, 27 to 30, 40 to 43	NO
Inventive step (IS)	Claims 9 to 26, 31 to 39, 44 to 46	YES
	Claims 1 to 8, 27 to 30, 40 to 43	NO
Industrial applicability (IA)	Claims 1 to 46	YES
	Claims	NO

**2. Citations and explanations (Rule 70.7)**

**NOVELTY (N) Claims 1 to 8**

D1: AU 80655/87 (606087) B

The reduction of isoflavone (I) to form the isoflavanol (II) by hydrogenation is anticipated by D1. Claim 1 remains a broad claim to this hydrogenation without delimiting features. D1 discloses the hydrogenation of isoflavone (IIa) to form isoflavanol (IIc) on page 16 lines 1 to 8. See the bottom of page 14 for formula (IIa). There is no inhibition on the person skilled in the art to enable this disclosure. Nor is there any inhibition on her from looking at references within the text of the anticipating specification if they are needed to achieve the disclosed result.

**INVENTIVE STEP (IS) Claims 1 to 8**

See above.

**NOVELTY (N) Claims 27 to 30**

The reduction of compounds of formula (III) to form compounds of formula (V) by hydrogenation is anticipated by D1. See the reduction of compounds of formula (III) to compounds of formula (I) on page 10 part (b) and page 16 process (b). There is no inhibition on the person skilled in the art to enable this disclosure, or to do so with recourse to the embedded references if necessary.

**INVENTIVE STEP (IS) Claims 27 to 30**

See above.

**NOVELTY (N) Claim 40**

Given the breadth of claims 1 and 27 entrained their anticipation, this claim is anticipated also as compounds of formula (II) and (V), respectively, are made in D1 in the guise of compounds of formula (IIc) and (I) respectively.

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

**Continuation of V****INVENTIVE STEP (IS) Claim 40**

As above.

**NOVELTY (N) Claim 41 to 43**

The proviso does not exclude the generic and specific disclosure of compounds in D1 which correspond to those of formula (V). Page 1 discloses formula (I) with RO as hydroxy, lower alkoxy, lower alkanoyloxy while one of R', R'' is hydroxy, lower alkoxy, lower alkanoyloxy or lower alkyl and the other is hydrogen. These correspond to R1, R6 and R7. Compounds of formula (V) with R1 beyond hydroxy or acetoxy and R6 beyond hydrogen, hydroxy or acetoxy and R7 beyond H, OH, methyl or methoxy are not excluded by the proviso bridging pages 46 and 47.

Specific examples are also not excluded. Examples 18, 22, 24 can have R4 as methoxy. Examples 36, 39 can have R4 as methyl. Example 41 can have R4 as H. Example 43 has R6 as n-hexyl. Examples 44, 45 can have R4 as fluoro. Example 47, 59, 61 has R3 or R4 as ethoxycarbonyl. Example 48 can have R4 as trifluoromethyl. Example 49 has R1 as methoxy. Examples 52, 55 can have R4 as chloro. Examples 53, 54 can have R4 as trifluoromethyl. Example 63 has R3 or R4 as methylsulfonyl. Example 64 has R3 or R4 as t-butyl. Example 68 has R3 or R4 as n-propylsulfonyl.

The proviso does not exclude the generic disclosure of compounds in D1 which corresponds to those of formula (II) at all. See D1's formula (IIc) on page 16 with the radicals defined on page 1.

The proviso does not exclude the generic disclosure of compounds in D1 which corresponds to those of formula (III) at all. See D1's formula (III) on page 10 with the radicals defined on page 1.

The proviso does not exclude all the generic disclosure of compounds in D1 which corresponds to those of formula (IV). See D1's formula (IIb) on page 15 with the radicals defined on page 1.

Specific examples are also not excluded. Examples 8, 9 have R2 as methyl. Example 10 has R2, R7 as methyl. Example 11 to 13 and 16 has R7 as methyl. The starting reagents in example 16, 19, 23 to 25, 28 have R7 as methyl. Example 26's starting benzopyran-4-one has R2, R7 as methyl. In examples 36, 39, they have R3 or R4 as methyl. In example 43, it has R6 as n-hexyl. In example 47, it has R3 or R4 as ethoxycarbonyl and R7 as methyl. In example 48, it has R7 as methyl and R3 or R4 as trifluoromethyl. In examples 49 and 50, they have R2 as methyl. In examples 53 and 54, they have R3 or R4 as trifluoromethyl. In example 58, it has R2 as isopropyl. In example 61, it has R3 or R4 as ethoxycarbonyl. In example 63, it has R3 or R4 as methylsulfonyl. In example 64, it has R3 or R4 as t-butyl. In example 68, R3 or R4 is n-propylsulfonyl.

**INVENTIVE (IS) Claim 41 to 43**

As above.

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38. A method of claim 37, wherein the compound of formula V is 4',7-diacetoxylflavan (equol diacetate) or 4',7-dihydroxyisoflavan (equol).

39. Methods substantially as hereinbefore described especially with reference to the Examples.

40. Compounds of formula II or formula III or formula IV or formula V when prepared by a method of any preceding claim.

41. A compound of the formulae II, III, IV or V,  
wherein

R<sub>1</sub> is hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, thio, alkylthio, or halo,

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, OS(O)R<sub>9</sub>, alkyl, aryl, thio, alkylthio or halo, and

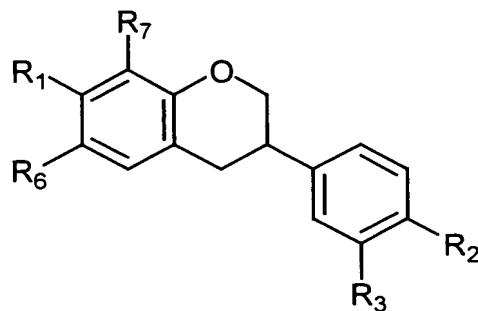
R<sub>9</sub> is alkyl, fluoroalkyl or arylalkyl

with the proviso that

at least one of R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> is not hydrogen, or

when R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are all hydrogen, then R<sub>3</sub> is hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, OS(O)R<sub>9</sub>, alkyl, aryl, thio, alkylthio or halo,

provided that compounds of the formula



wherein

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R<sub>1</sub> is hydroxy or acetoxy,

R<sub>2</sub> is hydrogen, hydroxy, acetoxy, methoxy, methyl, isopropyl or halo,

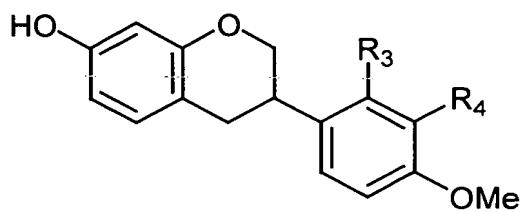
R<sub>3</sub> is hydrogen, methoxy, methyl, halo or trifluoromethyl,

R<sub>6</sub> is hydrogen, hydroxy or acetoxy, and

R<sub>7</sub> is hydrogen, hydroxy, methyl or methoxy

are specifically excluded,

provided that compounds of the formula



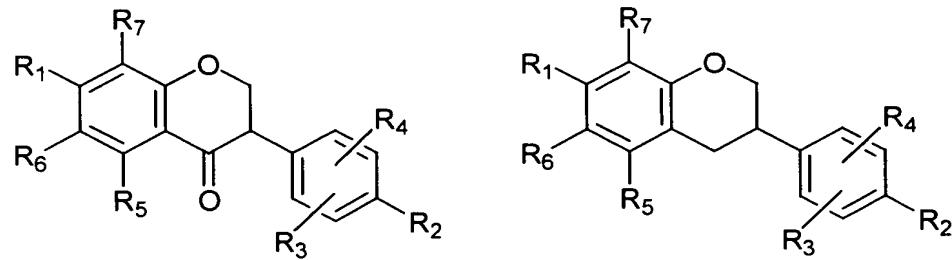
wherein

R<sub>3</sub> is hydroxy or methoxy, and

R<sub>4</sub> is hydrogen or methoxy

are specifically excluded,

provided that compounds of the formulae



wherein

R<sub>1</sub> is hydroxy, methoxy, ethoxy, methylthio or halogen, and

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>7</sub> are independently hydrogen, hydroxy, methoxy, ethoxy, methylthio or halogen,

are specifically excluded, and

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provided that the compounds

4',7-Dihydroxy-3',5'-dimethoxyisoflavan-4-one

4',5-Dimethoxy-7-hydroxy-8-methylisoflavan-4-one

2',7-Dihydroxy-4',8-dimethoxyisoflavan-3-ene

are specifically excluded.

42. A compound of claim 41,

wherein

R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

R<sub>2</sub> and R<sub>3</sub> are independently hydrogen, hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are hydrogen,

R<sub>7</sub> is hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or halo, and

R<sub>9</sub> is methyl, ethyl, propyl, isopropyl, trifluoromethyl or benzyl.

43. A compound of claim 41,

wherein

R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

R<sub>2</sub> and R<sub>3</sub> are independently hydrogen, hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

R<sub>5</sub> is OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or halo,

R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub>, and R<sub>8</sub> are hydrogen, and

R<sub>9</sub> is methyl, ethyl, propyl, isopropyl, trifluoromethyl or benzyl.

44. A compound of formula I selected from the group consisting of:

4',7,8-Triacetoxyisoflavone

7,8-Diacetoxy-4'-methoxyisoflavone

4',7-Diacetoxy-8-methylisoflavone

3',7-Diacetoxy-8-methylisoflavone

7-Acetoxy-4'-methoxy-8-methylisoflavone

4',7-Diacetoxy-3'-methoxy-8-methylisoflavone

4',5,7-Triacetoxyisoflavone

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45. A compound of formula II selected from the group consisting of:

- 4',7,8-Triacetoxyisoflavan-4-ol
- 7,8-Diacetoxy-4-methoxyisoflavan-4-ol
- 4',7-Diacetoxy-8-methylisoflavan-4-ol
- 3',7-Diacetoxy-8-methylisoflavan-4-ol
- 7-Acetoxy-4'-methoxy-8-methylisoflavan-4-ol
- 4',7-Diacetoxy-3'-methoxy-8-methylisoflavan-4-ol
- 4',5,7-Triacetoxyisoflavan-4-ol
  
- 4',7,8-Trihydroxyisoflavan-4-ol
- 7,8-Dihydroxy-4-methoxyisoflavan-4-ol
- 4',7-Dihydroxy-8-methylisoflavan-4-ol
- 3',7-Dihydroxy-8-methylisoflavan-4-ol
- 7-Hydroxy-4'-methoxy-8-methylisoflavan-4-ol
- 4',7-Dihydroxy-3'-methoxy-8-methylisoflavan-4-ol
- 4',5,7-Trihydroxyisoflavan-4-ol

46. A compound of formula III selected from the group consisting of:

- 4',7,8-Triacetoxydehydroequol (4',7,8-Triacetoxyisoflav-3-ene)
- 7,8-Diacetoxy-4-methoxydehydroequol (7,8-Diacetoxy-4-methoxyisoflav-3-ene)
- 4',7-Diacetoxy-8-methylisoflav-3-ene
- 3',7-Diacetoxy-8-methylisoflav-3-ene
- 7-Acetoxy-4'-methoxy-8-methylisoflav-3-ene
- 4',7-Diacetoxy-3'-methoxy-8-methylisoflav-3-ene
- 4',5,7-Triacetoxyisoflav-3-ene

- Isoflav-3-ene-4',7,8-triol
- 4'-Methoxyisoflav-3-ene-7,8-diol
- 8-Methylisoflav-3-ene-4',7-diol
- 8-Methylisoflav-3-ene-3',7-diol

Received 04 May 2001

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4'-Methoxy-8-methylisoflav-3-ene-7-ol

3'-Methoxy-8-methylisoflav-3-ene-4',7-diol

Isoflav-3-ene-4',5,7-triol

38. A method of claim 37, wherein the compound of formula V is 4',7-diacetoxyisoflavan (equol diacetate) or 4',7-dihydroxyisoflavan (equol).
- 5 39. Methods substantially as hereinbefore described especially with reference to the Examples.

40. Compounds of formula II or formula III or formula IV or formula V when prepared by a method of any preceding claim.

10

41. A compound of the formula I, II, III, IV or V,

wherein

R<sub>1</sub> is hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, thio, alkylthio, or halo,

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>,  
15 OS(O)R<sub>9</sub>, alkyl, aryl, thio, alkylthio or halo, and

R<sub>9</sub> is alkyl, fluoroalkyl or arylalkyl

with the proviso that

at least one of R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> is not hydrogen, or

when R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are all hydrogen, then R<sub>3</sub> is hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, OS(O)R<sub>9</sub>, alkyl,  
20 aryl, thio, alkylthio or halo.

42. A compound of claim 41,

wherein

R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

25 R<sub>2</sub> and R<sub>3</sub> are independently hydrogen, hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are hydrogen,

R<sub>7</sub> is hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or halo, and

R<sub>9</sub> is methyl, ethyl, propyl, isopropyl, trifluoromethyl or benzyl.

30 43. A compound of claim 41,

wherein

R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

R<sub>2</sub> and R<sub>3</sub> are independently hydrogen, hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

R<sub>5</sub> is OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or halo,  
R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub>, and R<sub>8</sub> are hydrogen, and  
R<sub>9</sub> is methyl, ethyl, propyl, isopropyl, trifluoromethyl or benzyl.

5 44. A compound of claim 41 selected from the group consisting of:

- 4',7,8-Triacetoxyisoflavone
- 7,8-Diacetoxy-4'-methoxyisoflavone
- 4',7-Diacetoxy-8-methylisoflavone
- 3',7-Diacetoxy-8-methylisoflavone
- 10 7-Acetoxy-4'-methoxy-8-methylisoflavone
- 4',7-Diacetoxy-3'-methoxy-8-methylisoflavone
- 4',5,7-Triacetoxyisoflavone
- 4',7,8-Triacetoxyisoflavan-4-ol
- 15 7,8-Diacetoxy-4-methoxyisoflavan-4-ol
- 4',7-Diacetoxy-8-methylisoflavan-4-ol
- 3',7-Diacetoxy-8-methylisoflavan-4-ol
- 7-Acetoxy-4'-methoxy-8-methylisoflavan-4-ol
- 4',7-Diacetoxy-3'-methoxy-8-methylisoflavan-4-ol
- 20 4',5,7-Triacetoxyisoflavan-4-ol
- 4',7,8-Trihydroxyisoflavan-4-ol
- 7,8-Dihydroxy-4-methoxyisoflavan-4-ol
- 4',7-Dihydroxy-8-methylisoflavan-4-ol
- 25 3',7-Dihydroxy-8-methylisoflavan-4-ol
- 7-Hydroxy-4'-methoxy-8-methylisoflavan-4-ol
- 4',7-Dihydroxy-3'-methoxy-8-methylisoflavan-4-ol
- 4',5,7-Trihydroxyisoflavan-4-ol
- 30 4',7,8-Triacetoxydehydroequol (4',7,8-Triacetoxyisoflav-3-ene)
- 7,8-Diacetoxy-4-methoxydehydroequol (7,8-Diacetoxy-4-methoxyisoflav-3-ene)
- 4',7-Diacetoxy-8-methylisoflav-3-ene
- 3',7-Diacetoxy-8-methylisoflav-3-ene

7-Acetoxy-4'-methoxy-8-methylisoflav-3-ene

4',7-Diacetoxy-3'-methoxy-8-methylisoflav-3-ene

4',5,7-Triacetoxyisoflav-3-ene

5 Isoflav-3-ene-4',7,8-triol

4'-Methoxyisoflav-3-ene-7,8-diol

8-Methylisoflav-3-ene-4',7-diol

8-Methylisoflav-3-ene-3',7-diol

4'-Methoxy-8-methylisoflav-3-ene-7-ol

10 3'-Methoxy-8-methylisoflav-3-ene-4',7-diol

Isoflav-3-ene-4',5,7-triol

4',7-Dihydroxy-8-methylisoflavan-4-ol

7-Hydroxy-4'-methoxy-8-methylisoflavan-4-ol

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> :	A1	(11) International Publication Number: <b>WO 00/49009</b>
C07D 311/36, 311/38, 311/04, 311/56		(43) International Publication Date: 24 August 2000 (24.08.00)
(21) International Application Number: PCT/AU00/00103		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 15 February 2000 (15.02.00)		
(30) Priority Data: PP 8685 15 February 1999 (15.02.99) AU		
(71) Applicant ( <i>for all designated States except US</i> ): NOVOGEN RESEARCH PTY. LTD. [AU/AU]; 140 Wicks Road, North Ryde, NSW 2113 (AU).		
(72) Inventors; and		
(75) Inventors/Applicants ( <i>for US only</i> ): HEATON, Andrew [AU/AU]; 2/46-48 Abbotsford Parade, Abbotsford, NSW 2046 (AU). KUMAR, Naresh [AU/AU]; 33 White Avenue, Maroubra, NSW 2035 (AU).		Published <i>With international search report.</i>
(74) Agents: HEISEY, Ross, Mitchell et al.; Davies_Collison_Cave, Level 10, 10 Barrack Street, Sydney, NSW 2000 (AU).		

**(54) Title:** PRODUCTION OF ISOFLAVONE DERIVATIVES**(57) Abstract**

Methods for the hydrogenation of isoflavones are described which provide access to workable quantities of isoflavan-4-ols, isoflav-3-enes, and isoflavans. The isoflavone derivatives can be obtained in high purity and in near quantitative yields whilst employing pharmaceutically acceptable reagents and solvents.

**FOR THE PURPOSES OF INFORMATION ONLY**

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BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		

## PRODUCTION OF ISOFLAVONE DERIVATIVES

### Introduction

5 The present invention relates to the hydrogenation of isoflavones and products thereof. The invention also relates to the synthesis of phytoestrogenic isoflavone metabolites and derivatives from the hydrogenation products of isoflavones.

### Background of the Invention

10

Isoflavone metabolites possess a very wide range of important biological properties including oestrogenic effects (WO 98/08503). Isoflavone metabolites can be isolated from the urine of human volunteers subjected to diets rich in plant isoflavanoids such as soya, lentils, peas and beans.

15

In spite of the recently discovered biological significance of isoflavone metabolites there is not at present a general method suitable for the large scale synthesis of these metabolites. The few reported syntheses of these metabolites utilise either catalytic hydrogenation or hydrogen transfer reduction of the corresponding isoflavones. These reduction reactions are 20 found to be non-selective, extremely difficult to control and lead to mixtures of different products.

The reduction of 5,7-dihydroxyisoflavylium salts have been reported to give mixtures of isoflav-2-enes, isoflav-3-enes and isoflavans. The individual compounds are difficult to 25 separate and can be obtained only in low yields. Sodium borohydride reductions of isoflavones are known, see Ádám Major *et al. Liebigs Ann. Chem.* (1988) 555-558, however the reactions are low yielding, typically not clean and substituents on the basic isoflavone ring structure require tedious protective groups not affected by metal hydrides.

30 Chromatography is often required to separate the reaction products and only low yields of isoflavanones, isoflavan-4-ols, isoflavenes and isoflavans are obtained. The chromatography required is tedious and often impracticable for large scale reactions. Furthermore, attempts to improve the yield and purity of products obtained from

hydrogenation reactions has been met with limited success as evidenced by published results which are largely contradictory.

Solvents used in hydrogenation reactions of isoflavones reported in the literature include *N*-5 methylpyrrolidinone, see Liepa, A.J., *Aust. J. Chem.*, 1981, **34**, 2647-55. However this solvent is unsuitable for pharmaceutical preparations of isoflavone metabolites and derivatives because *N*-methylpyrrolidinone is a severe eye irritant and a possible carcinogen. Furthermore the high boiling point of the solvent makes it extremely difficult to remove after the reduction.

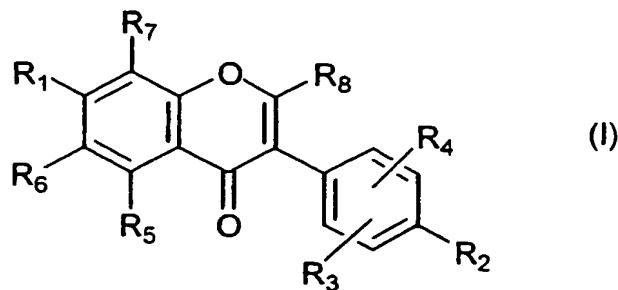
10

Isoflavan-4-ols are key intermediates in the synthesis of isoflavenes and accordingly there is a need for more efficient and reliable syntheses of isoflavan-4-ols, or at least comparable alternatives, acceptable than those known in the art. There is also a need for synthetic methods for isoflavone hydrogenation which utilise solvents pharmaceutically more 15 acceptable than those previously reported. Therefore it is an object of the present invention to overcome or at least alleviate one or more of the above-mentioned disadvantages of the prior art. It is an other object of the present invention to synthesise novel isoflavone metabolites and derivatives.

20 Surprisingly hydrogenation conditions have been found by the present inventors which enable the synthesis of isoflavone derivatives in good to excellent yields. In particular the conditions found by the present inventors allow for the hydrogenation of isoflavones to relatively pure tetrahydroisoflavan-4-ol products in excellent yields, and without the need for pharmaceutically unsuitable solvents and extensive chromatography in the 25 hydrogenation reactions.

### **Summary of the Invention**

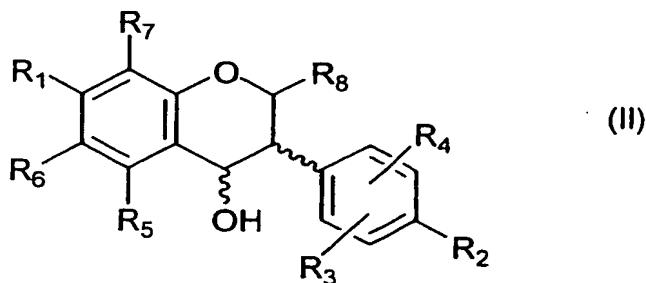
Thus the present invention provides a method for the hydrogenation of a compound of 30 formula I



wherein

- 10 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, OS(O)R<sub>9</sub>, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, and  
R<sub>9</sub> is alkyl, haloalkyl, aryl, arylalkyl or alkylaryl,  
to prepare a compound of formula II

15



wherein

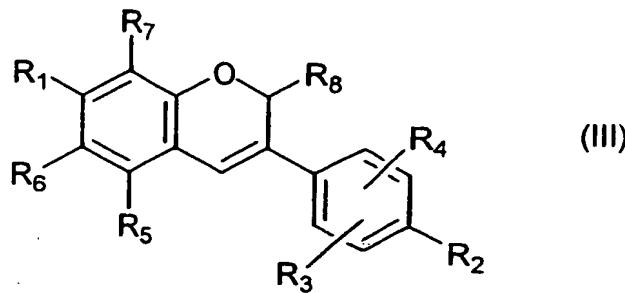
R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are as defined above.

25

The present invention also provides a method for the dehydration of a compound of formula II, which method may optionally include deprotection or transformation steps, to prepare a compound of the formula III

30

5

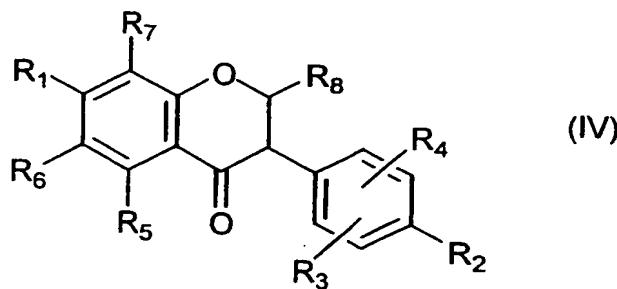


wherein

- 10 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, OS(O)R<sub>9</sub>, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, and  
R<sub>9</sub> is alkyl, haloalkyl, aryl, arylalkyl or alkylaryl.

- 15 The present invention also provides a method for the hydrogenation of a compound of formula I to prepare a compound of formula IV

20

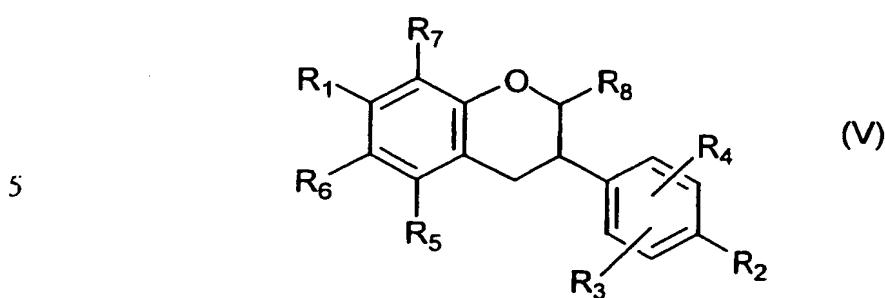


25 wherein

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are as defined above

The present invention also provides a method for the hydrogenation of a compound of formula III to prepare a compound of formula V

30



wherein

10 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are as defined above.

The present invention also provides compounds of formulae II, III, IV and V when prepared by a method described above and compositions comprising same.

15 The present invention also provides novel compounds of the formulae I, II, III, IV and V and compositions comprising same.

#### **Detailed Description of the Invention**

20 In the methods of the present invention, the starting isoflavone of formula I, the hydrogenation products isoflavan-4-ol of formula II, isoflavan-4-one of formula IV and isoflavan of formula V, and the dehydration product isoflav-3-ene of formula III preferably have the following substituents wherein

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>,

25 OS(O)R<sub>9</sub>, alkyl, aryl, arylalkyl, thio, alkylthio, bromo, chloro or fluoro, and  
R<sub>9</sub> is alkyl, fluoroalkyl or arylalkyl;

more preferably they have the following substituents wherein

R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

30 R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or arylalkyl,

R<sub>8</sub> is hydrogen, and

R<sub>9</sub> is methyl, ethyl, propyl, isopropyl or trifluoromethyl; and

most preferably they have the following substituents wherein

R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>7</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or  
5 arylalkyl,

R<sub>6</sub> and R<sub>8</sub> are hydrogen, and

R<sub>9</sub> is methyl.

The particularly preferred compounds of formula I are 4',7-diacetoxyisoflavone (daidzein  
10 diacetate) and 7-acetoxy-4'-methoxyisoflavone;

the particularly preferred compounds of formula II are 4',7-diacetoxyisoflavan-4-ol  
(tetrahydrodaidzein diacetate) and 7-acetoxy-4'-methoxyisoflavan-4-ol;

the particularly preferred compounds of formula III are 4',7-diacetoxyisoflav-3-ene  
(dehydroequol diacetate), 4',7-dihydroxyisoflav-3-ene (dehydroequol), 7-acetoxy-4'-  
15 methoxyisoflav-3-ene and 7-hydroxy-4'-methoxyisoflav-3-ene;

the particularly preferred compounds of formula IV are 4',7-diacetoxyisoflavan-4-one  
(diacetoxydihydrodaidzein) and 4',7-dihydroxyisoflavan-4-one (dihydrodaidzein); and

the particularly preferred compounds of formula V are 4',7-diacetoxyisoflavan (equol  
diacetate) and 4',7-dihydroxyisoflavan (equol).

20

The novel compounds of the formulae I, II, III, IV and V preferably have the following  
substituents wherein

R<sub>1</sub> is hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, thio, alkylthio, or halo,

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>,  
25 OS(O)R<sub>9</sub>, alkyl, aryl, thio, alkylthio or halo, and

R<sub>9</sub> is alkyl, fluoroalkyl or arylalkyl

with the proviso that

at least one of R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> is not hydrogen, or

when R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are all hydrogen, then R<sub>3</sub> is hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, OS(O)R<sub>9</sub>, alkyl,  
30 aryl, thio, alkylthio or halo; and

more preferably they have the following substituents wherein

R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

- R<sub>2</sub> and R<sub>3</sub> are independently hydrogen, hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,  
R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are hydrogen,  
R<sub>7</sub> is hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or halo, and  
R<sub>9</sub> is methyl, ethyl, propyl, isopropyl, trifluoromethyl or benzyl; or  
5 wherein  
R<sub>1</sub> is hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>,  
R<sub>2</sub> and R<sub>3</sub> are independently hydrogen, hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,  
R<sub>5</sub> is OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or halo,  
R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub>, and R<sub>8</sub> are hydrogen, and  
10 R<sub>9</sub> is methyl, ethyl, propyl, isopropyl, trifluoromethyl or benzyl.

Most preferably the novel compounds of formulae I, II and III are:

- 4',7,8-Triacetoxyisoflavone  
7,8-Diacetoxy-4'-methoxyisoflavone  
15 4',7-Diacetoxy-8-methylisoflavone  
3',7-Diacetoxy-8-methylisoflavone  
7-Acetoxy-4'-methoxy-8-methylisoflavone  
4',7-Diacetoxy-3'-methoxy-8-methylisoflavone  
4',5,7-Triacetoxyisoflavone  
20 4',7,8-Triacetoxyisoflavan-4-ol  
7,8-Diacetoxy-4-methoxyisoflavan-4-ol  
4',7-Diacetoxy-8-methylisoflavan-4-ol  
3',7-Diacetoxy-8-methylisoflavan-4-ol  
25 7-Acetoxy-4'-methoxy-8-methylisoflavan-4-ol  
4',7-Diacetoxy-3'-methoxy-8-methylisoflavan-4-ol  
4',5,7-Triacetoxyisoflavan-4-ol  
  
4',7,8-Trihydroxyisoflavan-4-ol  
30 7,8-Dihydroxy-4-methoxyisoflavan-4-ol  
4',7-Dihydroxy-8-methylisoflavan-4-ol  
3',7-Dihydroxy-8-methylisoflavan-4-ol  
7-Hydroxy-4'-methoxy-8-methylisoflavan-4-ol

4',7-Dihydroxy-3'-methoxy-8-methylisoflavan-4-ol

4',5,7-Trihydroxyisoflavan-4-ol

4',7,8-Triacetoxydehydroequol (4',7,8-Triacetoxyisoflav-3-ene)

5 7,8-Diacetoxy-4-methoxydehydroequol (7,8-Diacetoxy-4-methoxyisoflav-3-ene)

4',7-Diacetoxy-8-methylisoflav-3-ene

3',7-Diacetoxy-8-methylisoflav-3-ene

7-Acetoxy-4'-methoxy-8-methylisoflav-3-ene

4',7-Diacetoxy-3'-methoxy-8-methylisoflav-3-ene

10 4',5,7-Triacetoxyisoflav-3-ene

Isoflav-3-ene-4',7,8-triol

4'-Methoxyisoflav-3-ene-7,8-diol

8-Methylisoflav-3-ene-4',7-diol

15 8-Methylisoflav-3-ene-3',7-diol

4'-Methoxy-8-methylisoflav-3-ene-7-ol

3'-Methoxy-8-methylisoflav-3-ene-4',7-diol

Isoflav-3-ene-4',5,7-triol

20 4',7-Dihydroxy-8-methylisoflavan-4-ol

7-Hydroxy-4'-methoxy-8-methylisoflavan-4-ol

The term "alkyl" is taken to mean both straight chain and branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, tertiary butyl, and the like.

25 Preferably the alkyl group is a lower alkyl of 1 to 6 carbon atoms. The alkyl group may optionally be substituted by one or more of fluorine, chlorine, bromine, iodine, carboxyl, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-carbonyl, di-(C<sub>1</sub>-C<sub>4</sub>-alkyl)-amino-carbonyl, hydroxyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, formyloxy, C<sub>1</sub>-C<sub>4</sub>-alkyl-carbonyloxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, C<sub>3</sub>-C<sub>6</sub>-cylcoalkyl or phenyl.

30

The term "aryl" is taken to include phenyl and naphthyl and may be optionally substituted by one or more C<sub>1</sub>-C<sub>4</sub>-alkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>-alkoxy, carbonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyloxy or halo.

The term "halo" is taken to mean one or more halogen radicals selected from fluoro, chloro, bromo, iodo and mixtures thereof, preferably fluoro and chloro, more preferably fluoro. Reference to for example "haloalkyl" includes monohalogenated, dihalogenated and up to 5 perhalogenated alkyl groups. Preferred perhalogenated groups are trifluoromethyl and pentafluoroethyl.

The compounds of the invention include all salts, such as acid addition salts, anionic salts and zwitterionic salts, and in particular include pharmaceutically acceptable salts.

10

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

15

The hydrogenation is ideally preformed with hydrogen in the presence of a reduction catalyst and a solvent. The reaction is preferably conducted under hydrogen at a pressure of 1-20 atmospheres, more preferably 1-5 atmospheres. The reaction may be performed from 10 to 60°C and is typically carried out at room temperature.

20

The reaction time may range from 12 hours to 96 hours or more and is typically about 55 hours or more. Generally better yields and cleaner reactions are achieved with longer reaction times. It will be appreciated that reaction conditions may be varied depending on the individual nature of the compounds and the progress of the hydrogenation reaction.

25

The reduction catalysts may be selected from heterogeneous catalysts (whereby the catalyst is insoluble in the reaction medium) or homogenous catalysts (whereby the catalyst is soluble in the reaction medium). Examples of heterogeneous reduction catalysts include Raney nickel, palladium black, palladium hydroxide on carbon, palladium on activated 30 carbon (1% Pd to 30% Pd), palladium on alumina powder, palladium on various barium salts, sodium borohydride reduced nickel, platinum metal, platinum black, platinum on activated carbon (1% Pt to 10% Pt), platinum oxide, rhodium salts, ruthenium salts and their chiral salts and zinc oxide. Preferably the catalyst is palladium on activated carbon (1% Pd

to 10% Pd), more preferably about 5% palladium on carbon. Platinum oxide (Adam's catalyst) is also a very useful hydrogenation catalyst for the methods of the present invention to produce predominantly *cis*-isomers of isoflavan-4-ols.

5 Examples of homogeneous reduction catalysts include chlorotris (triphenylphosphine)rhodium, chloro(trisphenylphosphine)hydridoruthenium (II) and pentacyanocobaltate (II).

The solvents suitable for use in the present invention include but are not limited to C<sub>1</sub>-C<sub>8</sub> alcohols and polyols, alkyl acetates, tetrahydrofuran, ethers, dioxane and C<sub>1</sub>-C<sub>3</sub> acids. Preferably the solvent is a C<sub>1</sub>-C<sub>6</sub> alcohol or C<sub>1</sub>-C<sub>6</sub> alkyl acetate, more preferably methanol, ethanol or ethyl acetate, as well as propanol, isopropanol, butanol, isobutanol, secbutanol, tertiary butanol, methyl formate, ethyl formate and methyl acetate. Most preferably the solvent is absolute methanol, ethanol or ethyl acetate.

15

The present inventors have found that with a judicious choice of catalysts, solvents and optionally protecting groups, isoflavones are reduced cleanly and in high yields to corresponding isoflavanols. In particular the use of absolute methanol or ethanol as a solvent provided for very clean catalytic hydrogenation over 5% palladium on charcoal of 20 isoflavones to afford up to quantitative yields of isoflavanols. In methods where, for example, 10% palladium on charcoal is employed, the reaction can proceed more rapidly, at times being complete within 12 hours. The ratio of *cis*- and *trans*-isomers of the isoflavan-4-ol hydrogenation product can vary with the choice of catalysts and the nature of the isoflavone substitute. By varying the methods of the present invention it is possible to 25 influence the isomeric ratio achieved during the reduction process.

Of particular interest are isoflavones with oxygen substitution (or precursors to oxygen substitution) at the 4'- and 7-positions as reduction of these compounds leads to the biologically important dehydroequol or precursors thereof. A convenient starting material is 30 daidzein which is readily obtained by established routes.

It will be understood that some moieties on the isoflavone rings may require protection or derivatisation prior to being subjected to hydrogenation. For example it may be desirable to

protect free hydroxy moieties with groups such as an acetoxy group to assist in the solubility of the substituted isoflavones and/or their susceptibility to hydrogenation. Protecting groups can be carried out by well established methods known in the art, for example as described in *Protective Groups in Organic Synthesis*, T. W. Greene.

5

In particular the present inventors have found it is useful to protect hydroxy groups when present as esters or ethers prior to reduction, with acetoxy or methoxy groups most favoured. Acylation is preferably carried out with the hydroxy compounds in a solvent mixture of a carboxylic acid anhydride and base. Protecting free hydroxy groups prior to hydrogenation increases yields up to and including quantitative yields. The reaction products are generally cleaner and do not require a chromatography step in the purification and isolation of the hydrogenation products.

Thus surprisingly, tetrahydrodaidzein diacetate was obtained in quantitative yield when the catalytic hydrogenation of diacetoxydaidzein in ethanol was continued for 55 h. Spectroscopic analysis established the product to be a 1:1 mixture of *cis*- and *trans*-isomers. Pleasingly, no further reduction of tetrahydrodaidzein was observed even if the reduction was continued for longer periods of time.

20 In a similar manner it was also surprisingly found that the protected isoflavone 7-acetoxy-4'-methoxydaidzein smoothly and cleanly underwent hydrogenation in ethanol to afford a quantitative yield of a 1:1 mixture of *cis*- and *trans*-isomers of 7-acetoxy-4'-methoxyisoflavan-4-ol. This reaction appears to be quite general and was repeated on many different substrates in amounts of up to one half gram and more.

25

In this regard the inventors have found conditions which allow for the large scale generation of clean and near quantitative yields of isoflavan-4-ols compounds by hydrogenation of corresponding isoflavones. In particular, it has been found that kilogram quantities of diacetoxy daidzein undergo smooth and efficient reduction to the isomeric *cis*- and *trans*-30 4',7-diacetoxyisoflavan-4-ols. The isomeric ratios can be influenced by the percentage of palladium in the catalyst.

The *cis-/trans*-isomeric mixtures are able to be dehydrated to isoflav-3-enes without the need for separation. However, if desired, the mixtures are able to be separated by a variety of methods as set out below.

5 The mixture of *cis-* and *trans*-tetrahydrodaidzein compounds are able to be separated by preparative HPLC. This mode of separation is quite tedious and limited to small amounts of material. Since reasonable quantities of the diacetoxy isoflavanols were able to be prepared, fractional crystallisation was attempted to separate the *cis*- and *trans*-isomers. A single recrystallisation of the 1:1 mixture from ethanol gave predominantly *trans*-  
10 diacetoxytetrahydrodaidzein (50% yield: 73% purity) (*cis*-isomer 27%). Subsequent recrystallisations from ethanol afforded the pure *trans*- isomer in 25% overall yield.

Likewise the 7-acetoxy-4'-methoxyisoflavan-4-ol was able to be fractionally recrystallised to give the pure *trans*-isomer, with the filtrate containing increased proportions of the *cis*-  
15 isomer.

Most hydrogenations yielded 1:1 mixtures of *cis*- and *trans*-isoflavan-4-ols. However one derivative of note was 7-hydroxy-4'-methoxy-8-methylisoflavone, the hydrogenation of which afforded predominantly the *trans*- isomer in excellent yield.

20

Synthesis of tetrahydrodaidzein and related derivatives was achieved by removal of the protecting acetoxy groups under mild conditions, preferably with imidazole in ethanol at reflux. Tetrahydrodaidzein was isolated in 80% yield after crystallisation from aqueous ethanol.

25

Dehydration of isoflavan-4-ols leads to the unsaturated isoflav-3-enes. Thus reaction of a *cis-/trans*-mixture of isoflavan-4-ols with benzoyl chloride/dimethylformamide at 100°C has been reported in the literature by Liepa to give the desired isoflav-3-ene dehydration product. However this reaction could only be repeated in low yield. Dehydration may also  
30 be effected by treatment with acids such as sulfuric acid, hydrochloric acid, polyphosphoric acid, thionyl chloride and the like. Alternative methods of dehydration using *p*-toluenesulfonic acid or trifluoroacetic acid in refluxing dichloromethane were also investigated, but these methods also afforded the isoflavenes in low yields.

Generally the present inventors found the dehydration reagent of choice to be phosphorus pentoxide in dichloromethane, which can yield isoflavenes in yields of greater than 60%. The dehydration reactions can be carried out on the hydrogenation products directly, or 5 deprotected derivatives thereof.

Synthesis of dehydroequol was achieved by removal of the protecting acetoxy groups under mild conditions as described for the synthesis of tetrahydrodaidzein, and dehydroequol was purified by standard crystallisation solvent mixtures such as ethanol/water. Other isoflav-3-10 ene derivatives may be prepared by similar methods.

Hydrogen reduction of 4',7-diacetoxysdaidzein with Adam's catalyst (platinum(IV)oxide) in ethyl acetate under an atmosphere of hydrogen afforded 4',7-diacetoxytetrahydrodaidzein. However unlike the palladium-on-charcoal reduction in ethanol, reductions with Adam's 15 catalyst gave predominantly the *cis*-isomer of 4',7-diacetoxytetrahydrodaidzein.

In another embodiment of the invention, hydrogenation of 4',7-diacetoxysdaidzein with 5% palladium-on-charcoal in ethyl acetate as solvent under an atmosphere of hydrogen gave 4',7-diacetoxysdihydrodaidzein in excellent yield (80%). These conditions provide access to 20 isoflavan-4-ones from the corresponding isoflavones in good to excellent yields.

Access to isoflavan derivatives such as equol is possible by hydrogenation of isoflav-3-enes with, preferably, palladium-on-charcoal in an alkyl acetate solvent under an atmosphere of hydrogen. Excellent yields of 75% and more of the hydrogenated products are obtainable by 25 these methods. The products are clean and are readily recrystallised.

The surprising results obtained by the present inventors are in sharp contrast to those reported in the literature for other attempted hydrogenations of isoflavones. One such marked advantage is the use of alkyl acetates or alcohol solvents such as absolute methanol 30 or ethanol in the hydrogenation reactions: The isoflavanols prepared by the methods of the present invention are typically very crystalline and can be isolated in good purity, and without the need for chromatography. The isoflavanols can be converted to isoflav-3-enes by dehydration. Further deprotection or derivatisation steps can be employed by those

skilled in the art to obtain natural isoflavan-4-ones, isoflavans, isoflavenes, metabolites and novel derivatives thereof as required.

The invention is further described in and illustrated by the following Examples. The  
5 Examples are not to be construed as limiting the invention in any way.

## EXAMPLES

### Acetylation Reactions

10

#### **Example 1**

##### **4',7 Diacetoxydaidzein**

###### **Method A**

A mixture of daidzein (1.0g, 3.9 mmol), acetic anhydride (5 ml) and pyridine (5 ml) was left  
15 in the dark at room temperature for 24 h. The reaction mixture was poured into water (100 ml), stirred for 2h and then extracted with dichloromethane (3 x 50 ml). The dichloromethane layer was washed with water, dried over anhydrous sodium sulfate and evaporated. The white residue was crystallised from methanol to yield daidzein diacetate as white prisms (1.1 g, 83%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.32 (s, 3H,  $\text{OCOCH}_3$ ), 2.36 (s, 3H,  
20  $\text{OCOCH}_3$ ), 7.18 (d, 2H, J 9.2 Hz, ArH), 7.19 (d, 1H, J 9.0 Hz, H6), 7.31 (d, 1H, J 2.0 Hz  
H8), 7.59 (d, 2H, J 9.2 Hz, ArH), 8.00 (s, 1H, H2), 8.33 (d, 2H, J 8.2 Hz, ArH).

###### **Method B**

A mixture of daidzein (2.0 g, 7.9 mmol), acetic anhydride (10 ml) and pyridine (2 ml) was  
25 heated on an oil bath at 105-110 C for 1h. After cooling the mixture to room temperature, it was stirred for a further 30 min during which time the diacetate crystallised from the solution. The product was filtered, washed thoroughly with water and recrystallised from methanol to yield daidzein diacetate as colourless prisms (2.4 g, 90%).

30 **Example 2**

##### **7-acetoxy-4'-methoxyisoflavone**

A mixture of 7-hydroxy-4'-methoxyisoflavanone (2.0g, 7.5 mmol), acetic anhydride (10 ml) and pyridine (2 ml) was heated on an oil bath at 105-110 C for 1 hour. After cooling the

mixture to room temperature, it was poured into water (100 ml), stirred for 2 hours and then extracted with dichloromethane (3 x 50 ml). The dichloromethane layer was washed with water, dried over anhydrous sodium sulfate and evaporated. The white residue was crystallised from methanol to yield 7-acetoxy-4'-methoxyisoflavone as colourless prisms 5 (2.1g, 91%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.36 (s, 3H,  $\text{OCOCH}_3$ ), 3.84 (s, 3H,  $\text{OCH}_3$ ), 6.98 (d, 2H, J 8.7 Hz, ArH), 7.16 (dd, 1H, J 1.9 Hz 8.6 Hz, H6), 7.30 (d, 1H, J 1.9 Hz H8), 7.50 (d, 2H, J 8.7 Hz, ArH), 8.00 (s, 1H, H2), 8.32 (d, 1H, J 8.6 Hz, H5).

### Example 3

#### 10 3',7-Diacetoxysflavone

3',7-Diacetoxysflavone was prepared from 3',7-dihydroxyisoflavone (0.98g, 3.9 mmol), acetic anhydride (6 ml) and pyridine (1.1 ml) as described for 4',7-diacetoxysflavone. Yield: (1.0g, 77%) m.p. 152°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.31 and 2.36 (each s, 3H,  $\text{OCOCH}_3$ ), 7.14 (m, 1H, ArH), 7.18 (dd, 1H, J 2.0 Hz 8.6 Hz, H6), 7.31 (d, 1H, J 2.0 Hz H8), 7.37-7.45 (m, 15 3H, ArH), 8.03 (s, 1H, H2), 8.32 (d, 1H, J 8.6 Hz, H5). Mass spectrum: m/z 338 (M, 8%); 296 (53); 254 (100); 253 (60).

### Example 4

#### 7-Acetoxy-3'-methoxyisoflavone

20 7-Acetoxy-3'-methoxyisoflavone was prepared from 7-hydroxy-3'-methoxyisoflavone (1.7g, 6.3 mmol), acetic anhydride (6 ml) and pyridine (1.0 ml) as described for 4',7-diacetoxysflavone. Yield: (1.6g, 81%) m.p. 118°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.36 (s, 3H,  $\text{OCOCH}_3$ ), 3.85 (s, 3H, OMe), 6.95 (dd, 1H, J 2.0 Hz 8.3 Hz, H6), 6.70-7.40 (m, 5H, ArH), 8.01 (s, 1H, H2), 8.32 (d, 1H, J 8.7 Hz, H5).

25

### Example 5

#### 4',7-Diacetoxysflavone

4',7-Diacetoxysflavone was prepared from 4',7-dihydroxy-3'-methoxyisoflavone (0.37g, 1.3 mmol), acetic anhydride (2.5 ml) and pyridine (0.4 ml) as 30 described for 4',7-diacetoxysflavone. Yield: (0.36g, 75%) m.p. 197°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.33, 2.36 (each s, 3H,  $\text{OCOCH}_3$ ), 3.88 (s, 3H, OMe), 7.06-7.17 (m, 2H, ArH), 7.19 (dd,

1H, J 2.3 Hz 9.0 Hz, ArH), 7.32 (dd, 2H, J 2.3 Hz 7.6 Hz, ArH), 8.03 (s, 1H, H2), 8.32 (d, 1H, J 8.6 Hz, H5).

### Example 6

#### 5 7-Acetoxyisoflavone

7-Acetoxyisoflavone was prepared from 7-hydroxyisoflavone (2.6g, 10.9 mmol), acetic anhydride (16 ml) and pyridine (3.0 ml) as described for 4',7-diacetoxydaidzein. Yield: (2.5g, 82%) m.p. 133°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.36 (s, 3H,  $\text{OCOCH}_3$ ), 7.18 (dd, 1H, J 2.2 Hz 8.6 Hz, H6), 7.31 (d, 1H, J 2.2 Hz H8), 7.39-7.57 (m, 5H, ArH), 8.00 (s, 1H, H2), 8.33 10 (d, 1H, J 8.6 Hz, H5). Mass spectrum: m/z 280 (M, 28%); 237 (98); 238 (57).

### Example 7

#### 4',7,8-Triacetoxyisoflavone

A mixture of 4',7,8-trihydroxyisoflavone (1.4g, 5.2 mmol), acetic anhydride (8.4 ml) and 15 pyridine (2 ml) was heated on an oil bath at 105-110°C for 1h. After cooling the mixture to room temperature, it was stirred for a further 30 min during which time the diacetate crystallised from the solution. The product was filtered, washed thoroughly with water and recrystallised from ethyl acetate to yield 4',7,8-triacetoxyisoflavone as colourless prisms (1.49g, 73%) m.p. 190-192°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.32, 2.36, 2.42 (each s, 3H,  $\text{OCOCH}_3$ ), 7.18 (d, 2H, J 8.6 Hz, ArH), 7.28 (d, 1H, J 8.9 Hz, H6), 7.56 (d, 2H, J 8.6 Hz H8), 7.98 (s, 1H, ArH), 8.18 (d, 1H, J 8.9 Hz, H5).

### Example 8

#### 7,8-Diacetoxy-4'-methoxyisoflavone

25 7,8-Diacetoxy-4'-methoxyisoflavone was prepared from 7,8-dihydroxy-4'-methoxyisoflavone (0.82g, 2.9 mmol), acetic anhydride (4.9 ml) and pyridine (0.9 ml) as described for 4',7,8-triacetoxyisoflavone. Yield: (0.9g, 85%) m.p. 165°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.36, 2.42 (each s, 3H,  $\text{OCOCH}_3$ ), 3.84 (s, 3H,  $\text{OCH}_3$ ), 6.98 (d, 2H, J 9.0 Hz, ArH), 7.25 (d, 1H, J 8.7 Hz, H6), 7.48 (d, 2H, J 9.0 Hz H8), 7.95 (s, 1H, H2), 8.20 (d, 1H, J 9.1 Hz, H5). Mass spectrum: m/z 368 (M; 20%); 326 (15); 312 (18); 284 (80).

### Example 9

**4',7-Diacetoxy-8-methylisoflavone**

A mixture of 4',7-dihydroxy-8-methylisoflavone (2.9g, 10.8 mmol), acetic anhydride (18 ml) and pyridine (3 ml) was heated on an oil bath at 105-110°C for 1h. After cooling the mixture to room temperature, it was stirred for a further 30 min during which time the diacetate crystallised from the solution. The product was filtered, washed thoroughly with water and recrystallised from ethyl acetate to yield 4',7-diacetoxy-8-methylisoflavone as colourless prisms (3.2g, 84%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.31 (s, 3H,  $\text{CH}_3$ ), 2.32, 2.39 (each s, 3H,  $\text{OCOCH}_3$ ), 7.13 (d, 1H,  $J$  9.0 Hz, H6), 7.17 (d, 2H,  $J$  8.7 Hz, ArH), 7.59 (d, 2H,  $J$  8.7 Hz, ArH), 8.07 (s, 1H, H2), 8.19 (d, 1H,  $J$  8.7 Hz, H5).

10

**Example 10****3',7-Diacetoxy-8-methylisoflavone**

3',7-Diacetoxy-8-methylisoflavone was prepared from 3',7-dihydroxy-8-methylisoflavone (1.3g, 4.8 mmol), acetic anhydride (8 ml) and pyridine (1.5 ml) as described for 4',7-diacetoxy-8-methylisoflavone. Yield: (1.2g, 70%) m.p. 112°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.31 (s, 3H,  $\text{CH}_3$ ), 2.32, 2.39 (each s, 3H,  $\text{OCOCH}_3$ ), 7.13 (m, 2H, ArH), 7.37-7.45 (m, 3H, ArH), 8.1 (s, 1H, H2), 8.18 (d, 1H,  $J$  8.7 Hz, H5). Mass spectrum: m/z 352 (M, 6%); 310 (35); 268 (100); 267 (60).

20 **Example 11****7-Acetoxy-4'-methoxy-8-methylisoflavone**

7-Acetoxy-4'-methoxy-8-methylisoflavone was prepared from 7-hydroxy-4'-methoxy-8-methylisoflavanone (3.0g, 10.6 mmol), acetic anhydride (10 ml) and pyridine (2.0 ml) as described for 4',7-diacetoxy-8-methylisoflavone. Yield: (2.0g, 58%) m.p. 190-192°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.31 (s, 3H,  $\text{CH}_3$ ), 2.38 (s, 3H,  $\text{OCOCH}_3$ ), 3.84 (s, 3H, OMe), 6.98 (d, 2H,  $J$  8.7 Hz, ArH), 7.12 (d, 1H,  $J$  8.6 Hz, H6), 7.52 (d, 2H,  $J$  8.7 Hz, ArH), 8.03 (s, 1H, H2), 8.18 (d, 1H,  $J$  8.6 Hz, H5). Mass spectrum: 325 (M + 1, 13%); 324 (M, 58%); 282 (100); 281 (42).

30 **Example 12****4',7-Diacetoxy-3'-methoxy-8-methylisoflavone**

4',7-Diacetoxy-3'-methoxy-8-methylisoflavone was prepared from 4',7-dihydroxy-3'-methoxy-8-methylisoflavone (0.42g, 1.4 mmol), acetic anhydride (2.6 ml) and pyridine (0.5 ml) as described for 4',7-diacetoxy-8-methylisoflavone. Yield: (0.4g, 74%) m.p. 209°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.22 (s, 3H, CH<sub>3</sub>), 2.32, 2.39 (each s, 3H, OCOCH<sub>3</sub>), 3.89 (s, 3H, OMe), 5 7.07-7.11 (m, 2H, ArH), 7.13 (d, 1H, J 8.6 Hz, H6), 7.32 (d, 1H, J 1.5 Hz, ArH), 8.09 (s, 1H, H2), 8.18 (d, 1H, J 8.7 Hz, H5).

**Hydrogenation Reactions:- Isoflavone → Isoflavan-4-ol**

10

**Example 13**

**4',7-diacetoxytetrahydrodaidzein (4',7-Diacetoxyisoflavan-4-ol)**

**Method A**

Palladium-on-charcoal (5%, 0.08 g) was added to a suspension of 4',7-diacetoxydaidzein 15 (0.5 g, 1.5 mmol) in absolute ethanol (400 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 55 hours. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield 4',7-diacetoxytetrahydrodaidzein (0.51 g, 100%) in quantitative yield. A nuclear magnetic resonance spectrum revealed the product to be a clean 1:1 mixture of *cis*- and *trans*-4',7-20 diacetoxytetrahydrodaidzein.

The *cis*- and *trans*-isomers were able to be separated by fractional recrystallisation. A 1:1 mixture of *cis*- and *trans*-4',7-diacetoxytetrahydrodaidzein (0.17 g), prepared as above, was dissolved in excess absolute ethanol and concentrated on a rotary evaporator. At the first 25 sign of crystallisation, further concentration of ethanol was stopped and the flask was cooled in an ice-bath. The resulting crystals were filtered and washed with a small amount of cold absolute ethanol. A nuclear magnetic resonance spectrum of the product (0.08 g) revealed it to be a mixture *trans*-4',7-diacetoxytetrahydrodaidzein (73%) and *cis*-4',7-diacetoxytetrahydrodaidzein (27%). Further recrystallisations of the mixture from ethanol 30 yielded the pure *trans*-4',7-diacetoxytetrahydrodaidzein (0.04 g, 24%).

The filtrate yielded predominantly *cis*-isomer. Nuclear magnetic resonance spectroscopic analysis revealed the substance to be a mixture of *cis*-4',7-diacetoxytetrahydrodaidzein (73%) and *trans*-4',7-diacetoxytetrahydrodaidzein (27%).

5 For *trans*-4',7-Diacetoxylflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.28 (s, 3H,  $\text{OCOCH}_3$ ), 2.29 (s, 3H  $\text{OCOCH}_3$ ), 3.14 (ddd, 1H, J 3.7 Hz, 7.9 Hz, 9.1 Hz, H3), 4.24 (dd, 1H, J 9.1 Hz, 11.3 Hz, H2); 4.35 (dd, 1H, J 3.7 Hz, 11.3 Hz, H2), 4.87 (d, 1H, J 7.9 Hz, H4), 6.61 (d, 1H, J 2.3 Hz, H8), 6.70 (dd, 1H, J 2.3 Hz, 8.4 Hz, H6), 7.06 (d, 2H, J 8.6 Hz, ArH), 7.23 (d, 2H, J 8.4 Hz, ArH), 7.44 (dd, 1H, J 0.8 Hz, 8.4 Hz, H5).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 20.98 ( $\text{OCOCH}_3$ ), 46.18 10 (C3), 68.04 (C2), 69.01 (C4), 109.67 (C8), 114.26 (C6), 121.96, 128.96 (ArCH), 129.40 (C5).

For *cis*-4',7-Diacetoxylflavan-4-ol:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.28 (s, 3H,  $\text{OCOCH}_3$ ), 2.29 (s, 3H,  $\text{OCOCH}_3$ ), 3.30 (dt, 1H, J 3.4 Hz, J 11.8 Hz, H3), 4.31 (ddd, 1H, J 1.4 Hz, 3.6 Hz, 10.5 Hz, H2); 4.56 (dd, 1H, J 10.5 Hz, 11.8 Hz, H2), 4.75 (dd, 1H, J 1.3 Hz, 3.2 Hz, H4), 6.66 (dd, 1H, J 2.3 Hz, 8.7 Hz, H6), 6.69 (d, 1H, J 2.3 Hz, H8), 7.08 (d, 2H, J 8.6 Hz, ArH), 7.26 (d, 1H, 8.4 Hz, H5), 7.29 (d, 2H, J 8.6 Hz ArH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 20.98 ( $\text{OCOCH}_3$ ), 43.52 (C3), 64.10 (C2), 66.46 (C4), 110.08 (C6), 114.09 (C8), 121.82, 129.40 (ArCH), 131.10 (C5).

20

### Method B

Palladium-on-charcoal (5%, 3.1 g) was added to a suspension of 4',7-diacetoxylflavan-4-ol (30.0 g) in absolute methanol (3600 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 55 hours. The catalyst was removed by filtration through 25 Celite and the filtrate was evaporated *in vacuo* to yield 4',7-diacetoxylflavan-4-ol (29.5g, 96%). A nuclear magnetic resonance spectrum revealed the product to be a clean 2:1 mixture of *cis*- and *trans*-4',7-diacetoxylflavan-4-ol.

### Method C

30 Palladium-on-charcoal (10%, 3.0 g) was added to a suspension of 4',7-diacetoxylflavan-4-ol (30.1g) in absolute methanol (3600 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 15 hours. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield 4',7-diacetoxylflavan-4-ol

(28.5g, 94%). A nuclear magnetic resonance spectrum revealed the product to be a clean 1:1 mixture of *cis*- and *trans*-4',7-diacetoxytetrahydrodaidzein.

#### Method D

5 Palladium-on-charcoal (5%, 100g) was added to a suspension of 4',7-diacetoxydaidzein (980g) in absolute methanol (100L) and the mixture was stirred at room temperature under a hydrogen atmosphere for 78 hours. The catalyst was removed by filtration through a ceramic candle filtration apparatus and the filtrate was evaporated *in vacuo* to yield 4',7-diacetoxytetrahydrodaidzein (820g, 83%). A nuclear magnetic resonance spectrum revealed 10 the product to be a clean 2:1 mixture of *cis*- and *trans*-4',7-diacetoxytetrahydrodaidzein.

#### Example 14

##### Synthesis of 7-Acetoxy-4'-methoxyisoflavan-4-ol

Palladium-on-charcoal (5%, 0.08g) was added to a suspension of 7-acetoxy-4'-methoxyisoflavone (0.5g, 1.6 mmol) in absolute ethanol (400 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 55 hours. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield 7-acetoxy-4'-methoxyisoflavan-4-ol (0.51g, 100%) in quantitative yield. A nuclear magnetic resonance spectrum revealed the product to be a clean 1:1 mixture of *cis*- and *trans*-7-acetoxy-4'-methoxyisoflavan-4-ol. 20

The *cis*- and *trans*-isomers were able to be separated by fractional recrystallisation. A 1:1 mixture of *cis*- and *trans*-4',7-diacetoxytetrahydrodaidzein, prepared as above, was recrystallised three times from ethanol to yield pure *trans*-7-acetoxy-4'-methoxyisoflavan-4-ol. 25 The filtrate yielded predominantly *cis*-isomer.

For *trans*-7-Acetoxy-4'-methoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.31 (s, 3H,  $\text{OCOCH}_3$ ), 3.14 (dt, 1H,  $J$  3.8 Hz, 8.6 Hz, H3), 3.82 (s, 3H,  $\text{OCH}_3$ ), 4.25 (dd, 1H,  $J$  9.4 Hz, 11.3 Hz, H2); 4.37 (dd, 1H,  $J$  4.1 Hz, 11.3 Hz, H2), 4.93 (d, 1H,  $J$  7.8 Hz, H4), 6.63 (d, 1H,  $J$  2.3 Hz, H8), 6.73 (dd, 1H,  $J$  2.3 Hz, 8.3 Hz, H6), 6.93 (d, 2H,  $J$  8.7 Hz, ArH), 7.19 (d, 2H,  $J$  8.7 Hz, ArH), 7.51 (d, 1H,  $J$  7.9 Hz, H5).

For *cis*-7-Acetoxy-4'-methoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.30 (s, 3H,  $\text{OCOCH}_3$ ), 3.28 (dt, 1H, J 3.4 Hz, J 12.1 Hz, H3), 3.84 (s, 3H,  $\text{OCH}_3$ ), 4.36 (ddd, 1H, J 1.4 Hz, 3.8 Hz, 10.1 Hz, H2); 4.57 (dd, 1H, J 10.1 Hz, 11.3 Hz, H2), 4.75 (bs, 1H, H4), 6.58 (d, 1H, J 2.3 Hz, H8), 6.75 (dd, 1H, J 2.3 Hz, 8.3 Hz, H6), 6.96 (d, 2H, J 8.6 Hz, ArH), 7.25 (d, 2H, 8.6 Hz, ArH), 7.34 (d, 1H, J 8.3 Hz, H5).

### Example 15

#### 3'-7-Diacetoxyisoflavan-4-ol

Palladium-on-charcoal (5%, 0.03g) was added to a suspension of 3',7-diacetoxyisoflavanone 10 (0.2g, 0.6 mmol) in methanol (50 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 55h. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield 3'-7-diacetoxyisoflavan-4-ol in quantitative yield. A nuclear magnetic resonance spectrum revealed the product to be a clean 1 : 1 mixture of *cis*- and *trans*-3'-7-diacetoxyisoflavan-4-ol.

15

For *trans*-3'-7-diacetoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.31 and 2.32 (each s, 3H,  $\text{OCOCH}_3$ ), 3.17 (ddd, 1H, J 3.6 Hz, 8.6 Hz, 11.2 Hz, H3), 4.26 (dd, 1H, J 9.2 Hz, 11.6 Hz, H2); 4.33 (m, 1H, H2), 4.91 (d, 1H, J 7.9 Hz, H4), 6.60-6.73 (m, ArH), 6.97-7.16 (m, ArH), 7.25-7.48 (m, ArH).

20

For *cis*-3'-7-diacetoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.30 and 2.31 (each s, 3H,  $\text{OCOCH}_3$ ), 3.31 (dt, 1H, J 3.3 Hz, J 11.6 Hz, H3), 4.31 (m, 1H, H2); 4.57 (dd, 1H, J 10.6 Hz, 11.9 Hz, H2), 4.79 (bs, 1H, H4), 6.60-6.73 (m, ArH), 6.97-7.16 (m, ArH), 7.25-7.48 (m, ArH).

25

### Example 16

#### 7-Acetoxy-3'-methoxyisoflavan-4-ol

*Cis*- and *trans*-7-acetoxy-3'-methoxyisoflavan-4-ol was prepared from 7-acetoxy-3'-methoxyisoflavone (0.5g, 1.6 mmol) and palladium-on-charcoal (5%, 0.12g) in methanol 30 (100 ml) by the method described above.

For *trans*-7-acetoxy-3'-methoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.28 (s, 3H,  $\text{OCOCH}_3$ ), 3.15 (ddd, 1H, J 3.8 Hz, 8.3 Hz, 12.0 Hz, H3), 3.80 (s, 3H, OMe), 4.26 (dd, 1H, J 9.4 Hz, 11.3 Hz, H2); 4.32 (m, 1H, H2), 4.95 (d, 1H, J 7.9 Hz, H4), 6.60-6.93 (m, ArH), 7.23-7.33 (m, ArH), 7.49 (d, J 8.7 Hz, ArH).

5

For *cis*-7-acetoxy-3'-methoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.28 (s, 3H,  $\text{OCOCH}_3$ ), 3.30 (dt, 1H, J 3.3 Hz, J 11.7 Hz, H3), 4.31 (m, 1H, H2); 4.58 (dd, 1H, J 10.5 Hz, 11.7 Hz, H2), 4.81 (bs, 1H, H4), 6.60-6.93 (m, ArH), 7.23-7.33 (m, ArH), 7.49 (d, J 8.7 Hz, ArH).

## 10 Example 17

### **4',7-Diacetoxy-3'-methoxyisoflavan-4-ol**

*Cis*- and *trans*-4'-7-diacetoxy-3'-methoxyisoflavan-4-ol was prepared from 4'-7-diacetoxy-3'-methoxyisoflavone (0.25g, 0.7 mmol) and palladium-on-charcoal (5%, 0.06g) in methanol (50 ml) by the method described above.

15

For *trans*-4'-7-diacetoxy-3'-methoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.29, 2.31 (each s, 3H,  $\text{OCOCH}_3$ ), 3.17 (ddd, 1H, J 3.8 Hz, 8.7 Hz, 12.5 Hz, H3), 3.79 (s, 3H, OMe), 4.26 (dd, 1H, J 9.4 Hz, 11.3 Hz, H2); 4.32 (m, 1H, H2), 4.93 (d, 1H, J 7.9 Hz, H4), 6.62-6.73 (m, ArH), 6.81-6.91 (m, ArH), 6.99-7.05 (m, ArH), 7.30 (d, J 8.3 Hz, ArH), 7.48 (d, J 9.0 Hz, 20 ArH).

20

For *cis*-7-acetoxy-3'-methoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.31, 2.32 (each s, 3H,  $\text{OCOCH}_3$ ), 3.33 (dt, 1H, J 3.3 Hz, J 11.3 Hz, H3), 3.83 (s, 3H, OMe), 4.31 (m, 1H, H2); 4.58 (t, 1H, J 10.5 Hz, H2), 4.82 (bs, 1H, H4), 6.62-6.73 (m, ArH), 6.81-6.91 (m, ArH), 25 6.99-7.05 (m, ArH), 7.30 (d, J 8.3 Hz, ArH), 7.48 (d, J 9.0 Hz, ArH).

## Example 18

### **7-Acetoxyisoflavan-4-ol**

*Cis*- and *trans*-7-acetoxyisoflavan-4-ol was prepared from 7-acetoxyisoflavone (0.4g, 1.4 mmol) and palladium-on-charcoal (5%, 0.09g) in absolute methanol (60 ml). m.p. 90°C.

Mass spectrum: m/z 284 (M, 10%); 226 (42); 138 (100); 137 (58).

For *trans*-7-acetoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.29 (s, 3H,  $\text{OCOCH}_3$ ), 3.17 (m, 1H, H3), 4.27 (t, 1H, J 10.6 Hz, H2); 4.30 (m, 1H, H2), 4.97 (d, 1H, J 8.3 Hz, H4), 6.60-6.73 (m, ArH), 7.08 (d, J 8.7 Hz, ArH), 7.23-7.37 (m, ArH), 7.49 (d, J 8.7 Hz, ArH).

5 For *cis*-7-acetoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.30 (s, 3H,  $\text{OCOCH}_3$ ), 3.33 (dt, 1H, J 3.4 Hz, J 11.7 Hz, H3), 4.36 (m, 1H, H2); 4.62 (t, 1H, J 10.5 Hz, H2), 4.80 (bs, 1H, H4), 6.60-6.73 (m, ArH), 7.08 (d, J 8.7 Hz, ArH), 7.23-7.37 (m, ArH), 7.49 (d, J 8.7 Hz, ArH).

### Example 19

#### 10 4',7,8-Triacetoxyisoflavan-4-ol

Palladium-on-charcoal (5%, 0.07g) was added to a suspension of 4',7,8-triacetoxyisoflavone (0.5g, 1.3 mmol) in methanol (100 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 55h. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield 4',7,8-triacetoxyisoflavan-4-ol in 15 quantitative yield. A nuclear magnetic resonance spectrum revealed the product to be a clean 1:1 mixture of *cis*- and *trans*-4',7,8-triacetoxyisoflavan-4-ol. Mass spectrum: m/z 400 (M, 5%); 358 (12); 298 (12); 256 (24); 196 (20); 162 (70); 154 (100); 120 (80).

For *trans*-4',7,8-triacetoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.28, 2.29, 2.31 (each s, 3H, 20  $\text{OCOCH}_3$ ), 3.20 (m, 1H, H3), 4.27 (dd, 1H, H2); 4.37 (m, 1H, H2), 4.93 (d, 1H, J 7.9 Hz, H4), 6.78 (d, 1H, J 8.3 Hz, H8), 7.09 (m, ArH), 7.11-7.31 (m, ArH), 7.39 (d, 1H, J 8.7 Hz, ArH).

For *cis*-4',7,8-triacetoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.30, 2.31, 2.32 (each s, 3H, 25  $\text{OCOCH}_3$ ), 3.35 (m, 1H, H3), 4.38 (m, 1H, H2); 4.57 (t, 1H, J 10.6 Hz, H2), 4.75 (bs, 1H, H4), 6.78 (d, 1H, J 8.3 Hz, H8), 7.09 (m, ArH), 7.11-7.31 (m, ArH), 7.39 (d, 1H, J 8.7 Hz, ArH).

### Example 20

#### 30 7,8-Diacetoxy-4-methoxyisoflavan-4-

- 24 -

7,8-Diacetoxy-4-methoxyisoflavan-4-ol was prepared from 7,8-dihydroxy-4'-methoxyisoflavone (0.4g, 1.1 mmol) in methanol (120 ml) using palladium-on-charcoal (5%, 0.08g) by the method described above.

- 5 For *trans*-7,8-diacetoxy-4-methoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.29, 2.30 (each s, 3H,  $\text{OCOCH}_3$ ), 3.14 (ddd, 1H, J 3.9 Hz, 9.2Hz, 12.5 Hz, H3), 3.79 (s, 3H,  $\text{OCH}_3$ ), 4.24 (dd, 1H, J 9.6 Hz, 11.2 Hz, H2); 4.35 (m, 1H, H2), 4.92 (d, 1H, J 7.8 Hz, H4), 6.78 (d, 1H, J 8.6 Hz, H6), 6.90 (m, ArH), 7.13-7.22 (m, ArH), 7.38 (d, J 8.6 Hz, ArH).
- 10 For *cis*-7,8-diacetoxy-4-methoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.30, 2.31 (each s, 3H,  $\text{OCOCH}_3$ ), 3.29 (dt, 1H, J 3.0 Hz, J 12.0 Hz, H3), 3.80 (s, 3H,  $\text{OCH}_3$ ), 4.36 (m, 1H, H2); 4.57 (t, 1H, J 10.6 Hz, H2), 4.75 (bs, 1H, H4), 6.77 (d, 1H, J 8.6 Hz, H6), 6.90 (m, ArH), 7.13-7.22 (m, ArH), 7.38 (d, J 8.6 Hz, ArH).

15 **Example 21**

**4',7-Diacetoxy-8-methylisoflavan-4-ol**

Palladium-on-charcoal (5%, 0.12g) was added to a suspension of 4',7-diacetoxy-8-methylisoflavone (1.0g, 2.8 mmol) in methanol (200 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 55h. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield 4',7-diacetoxy-8-methylisoflavan-4-ol in quantitative yield, m.p. 135-37°C. A nuclear magnetic resonance spectrum revealed the product to be a clean 1:1 mixture of *cis*- and *trans*-4',7-diacetoxy-8-methylisoflavan-4-ol. Mass spectrum: 356 (M, 53%); 254 (86); 253 (100); 240 (80); 196 (37).

25

For *trans*-4',7-diacetoxy-8-methylisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.02 (s, 3H,  $\text{CH}_3$ ), 2.30, 2.31 (each s, 3H,  $\text{OCOCH}_3$ ), 3.15 (ddd, 1H, J 3.8 Hz, 8.6 Hz, 11.7, H3), 4.27 (dd, 1H, J 9.4 Hz, 11.3 Hz, H2); 4.39 (m, 1H, H2), 4.92 (d, 1H, J 7.5 Hz, H4), 6.64 (d, 1H, J 8.0 Hz, H6), 7.06-7.32 (m, ArH).

30

For *cis*-4',7-diacetoxy-8-methylisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.02 (s, 3H,  $\text{CH}_3$ ), 2.31, 2.32 (each s, 3H,  $\text{OCOCH}_3$ ), 3.28 (dt, 1H, J 3.4 Hz, J 11.7 Hz, H3), 4.40 (m, 1H, H2); 4.58

(dd, 1H, J 10.1 Hz, 11.7 Hz, H2), 4.78 (bs, 1H, H4), 6.67 (d, 1H, J 8.0 Hz, H6), 7.06-7.32 (m, ArH).

### Example 22

#### 5 3',7-Diacetoxy-8-methylisoflavan-4-ol

3',7-Diacetoxy-8-methylisoflavan-4-ol was prepared from 3',7-diacetoxy-8-methylisoflavone (0.25g, 0.7 mmol) in methanol (50 ml) using palladium-on-charcoal (5%, 0.06g) by the method described above.

10 For *trans*-3',7-diacetoxy-8-methylisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.03 (s, 3H,  $\text{CH}_3$ ), 2.30, 2.32 (each s, 3H,  $\text{OCOCH}_3$ ), 3.18 (ddd, 1H, J 3.8 Hz, 8.3 Hz, 12.1 Hz, H3), 4.28 (dd, 1H, J 9.0 Hz, 10.9 Hz, H2), 4.39 (m, 1H, H2), 4.94 (d, 1H, J 8.7 Hz, H4), 6.65 (d, 1H, J 7.9 Hz, H6), 6.98-7.39 (m, ArH).

15 For *cis*-3',7-diacetoxy-8-methylisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.05 (s, 3H,  $\text{CH}_3$ ), 2.30, 2.32 (each s, 3H,  $\text{OCOCH}_3$ ), 3.32 (dt, 1H, J 3.4 Hz, J 12.0 Hz, H3), 4.39 (m, 1H, H2); 4.59 (dd, 1H, J 10.5 Hz, 11.7 Hz, H2), 4.80 (bs, 1H, H4), 6.68 (d, 1H, J 8.3 Hz, H6), 6.98-7.39 (m, ArH).

20 Example 23

#### 7-Acetoxy-4'-methoxy-8-methylisoflavan-4-ol

7-Acetoxy-4'-methoxy-8-methylisoflavan-4-ol was prepared from 7-hydroxy-4'-methoxy-8-methylisoflavone (0.25g, 0.8 mmol) in methanol (50 ml) using palladium-on-charcoal (5%, 0.08g) by the method described above. This hydrogenation reaction predominantly yielded 25 the *trans*-isomer.

For *trans*-7-Acetoxy-4'-methoxy-8-methylisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.02 (s, 3H,  $\text{CH}_3$ ), 2.32 (s, 3H,  $\text{OCOCH}_3$ ), 3.11 (ddd, 1H, J 3.8 Hz, 9.4 Hz, 12.1 Hz, H3), 3.80 (s, 3H, OMe), 4.25 (dd, 1H, J 9.4 Hz, 11.3 Hz, H2); 4.40 (dd, 1H, J 3.8 Hz, 12.6 Hz, H2), 4.92 (bd, 30 1H, H4), 6.67 (d, 1H, J 8.3 Hz, H6), 6.89 (d, 2H, J 8.7 Hz, ArH), 7.16 (d, 2H, J 8.7 Hz, ArH), 7.34 (d, 1H, J 8.3 Hz, H5).

**Example 24****4',7-Diacetoxy-3'-methoxy-8-methylisoflavan-4-ol**

4',7-Diacetoxy-3'-methoxy-8-methylisoflavan-4-ol was prepared from 4',7-diacetoxy-3'-methoxy-8-methylisoflavone (0.25g, 0.7 mmol) in methanol (50 ml) using palladium-on-charcoal (5%, 0.07g) by the method described above.

For *trans*-4',7-diacetoxy-3'-methoxy-8-methylisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.05 (s, 3H,  $\text{CH}_3$ ), 2.30, 2.32 (each s, 3H,  $\text{OCOCH}_3$ ), 3.18 (ddd, 1H,  $J$  3.8 Hz, 8.3 Hz, 11.4 Hz, H3), 3.79 (s, 3H, OMe), 4.28 (dd, 1H,  $J$  9.0 Hz, 11.3 Hz, H2); 4.41 (m, 1H, H2), 4.93 (d, 1H,  $J$  7.9 Hz, H4), 6.64 (d, 1H,  $J$  7.9 Hz, H6), 6.75-6.92 (m, ArH), 7.00 (d, 1H,  $J$  7.9 Hz, ArH), 7.16 (d, 1H,  $J$  8.3 Hz, ArH).

For *cis*-3',7-diacetoxy-8-methylisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.05 (s, 3H,  $\text{CH}_3$ ), 2.30, 2.32 (each s, 3H,  $\text{OCOCH}_3$ ), 3.29 (dt, 1H,  $J$  3.4 Hz,  $J$  11.7 Hz, H3), 4.40 (m, 1H, H2); 4.59 (t, 1H,  $J$  10.5 Hz, H2), 4.81 (bs, 1H, H4), 6.67 (d, 1H,  $J$  7.9 Hz, H6), 6.75-6.92 (m, ArH), 7.03 (d, 1H,  $J$  8.3 Hz, ArH), 7.33 (d, 1H,  $J$  8.3 Hz, ArH).

**Dehydration Reactions****20 Example 25****4',7-Diacetoxydehydroequol (4',7-Diacetoxyisoflav-3-ene)****Method A**

Distilled trifluoroacetic acid (0.1 ml) was added to a solution of *cis*- and *trans*-4',7-diacetoxytetrahydrodaidzein (0.1g) in dry distilled dichloromethane (15 ml) and the mixture 25 was refluxed under argon. Progress of the reaction was monitored by thin layer chromatography and further 0.1 ml portions of trifluoroacetic acid were added. After refluxing for 4 hours, the reaction mixture was cooled and washed successively with saturated sodium bicarbonate solution, water and brine. The resulting organic phase was dried, concentrated, chromatographed and crystallised to yield 4',7-diacetoxydehydroequol 30 as colourless prisms (0.034g, 35%).  $^1\text{H}$  NMR ( $\text{CDCl}_3 + \text{d}_6\text{-DMSO}$ ):  $\delta$  2.29 (s, 3H,  $\text{OCOCH}_3$ ), 2.31 (s, 3H,  $\text{OCOCH}_3$ ), 5.15 (s, 2H, H2), 6.62 (bs, 1H, H4), 6.65 (dd, 1H,  $J$  2.1

Hz 8.2 Hz, H6), 6.75 (bs, 1H, H8), 7.06 (d, 1H, J 8.2 Hz H5), 7.12 (d, 2H, J 8.2 Hz, ArH), 7.43 (d, 2H, J 8.2 Hz, ArH).

### Method B

5 *p*-Toluenesulfonic acid (0.02 g) was added to a solution of *cis*- and *trans*-4'7-diacetoxytetrahydrodaidzein (0.1 g) in dry distilled dichloromethane (15 ml) and the mixture was refluxed under argon. Progress of the reaction was monitored by thin layer chromatography and after 4h at reflux, the reaction mixture was passed through a short column of silica gel and the eluant recrystallised from ethanol to yield 4',7-10 diacetoxydehydroequol as colourless prisms (0.025 g, 26%).

### Method C

Phosphorous pentoxide (5g) was added with stirring to a solution of *cis*- and *trans*-4',7-diacetoxytetrahydrodaidzein (1.0g) in dry dichloromethane (80 ml). The mixture was stirred 15 at room temperature for 2 hours and filtered through a pad of Celite. The dichloromethane solution was concentrated and chromatographed on silica gel to yield 4',7-diacetoxydehydroequol as colourless prisms (0.64g, 67%).

### Example 26

#### 20 7-Acetoxy-4'-methoxyisoflav-3-ene

Phosphorus pentoxide (1.0g) was added with stirring to a solution of *cis*- and *trans*-7-acetoxy-4'-methoxyisoflavan-4-ol (0.1g, 0.3 mmol) in dry dichloromethane (20 ml). The mixture was stirred at room temperature for 2 hours and filtered through a pad of Celite. The organic phase was concentrated and chromatographed on silica gel to yield 7-acetoxy-25 4'-methoxyisoflav-3-ene (0.04g, 42%). 1H NMR (CDCl<sub>3</sub>); δ 2.28 (s, 3H, OCOCH<sub>3</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 5.14 (s, 2H, H2), 6.61 (dd, 1H, J 2.3 Hz 6.4 Hz, H6), 6.65 (d, 1H, J 2.3 Hz, H8), 6.69 (bs, 1H, H4), 6.92 (d, 2H, J 9.0 Hz ArH), 7.04 (d, 1H, J 7.9 Hz, H5), 7.37 (d, 2H, J 9.0 Hz, ArH).

#### 30 Example 27

##### 3',7-Diacetoxydehydroequol (3',7-Diacetoxyisoflav-3-ene)

3',7-Diacetoxyisoflav-3-ene was prepared from *cis*- and *trans*-3',7-diacetoxyisoflavan-4-ol (0.2g, 0.6 mmol) in dry dichloromethane (50 ml) using phosphorus pentoxide (2.0g). Yield:

(0.09g, 48%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.29 and 2.32 (each s, 3H,  $\text{OCOCH}_3$ ), 5.14 (s, 2H, H2), 6.61 (d, 1H, J 2.3 Hz, H8), 6.66 (dd, 1H, J 2.3 Hz 7.9 Hz, H6), 6.79 (bs, 1H, H4), 7.02-7.15 (m, 3H, ArH), 7.25-7.44 (m, 2H, ArH).

## 5 Example 28

### **7-Acetoxy-3'-methoxydehydroequol (7-Acetoxy-3'-methoxyisoflav-3-ene)**

7-Acetoxy-3'-methoxyisoflav-3-ene was prepared from *cis*- and *trans*-7-acetoxy-3'-methoxyisoflavan-4-ol (0.25g, 0.8 mmol) in dry dichloromethane (20 ml) using phosphorus pentoxide (2.0g). Yield: (0.15g, 63%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.28 (s, 3H,  $\text{OCOCH}_3$ ), 3.85 (s, 3H, OMe), 5.15 (s, 2H, H2), 6.60-6.67 (m, 2H, ArH), 6.78 (bs, 1H, H4), 6.84-7.06 (m, 4H, ArH), 7.35 (t, 1H, J 8.6 Hz, ArH).

## Example 29

### **4',7-Diacetoxy-3'-methoxyisoflav-3-ene**

15 4',7-Diacetoxy-3'-methoxyisoflav-3-ene was prepared from *cis*- and *trans*-4',7-diacetoxy-3'-methoxyisoflavan-4-ol (0.20g, 0.5 mmol) in dry dichloromethane (20 ml) using phosphorus pentoxide (2.0g). Yield: (0.11g, 58%).

## Example 30

### **20 7-Acetoxyisoflav-3-ene**

7-acetoxyisoflav-3-ene was prepared from *cis*- and *trans*-7-acetoxyisoflavan-4-ol (0.4g, 1.4 mmol) in dry dichloromethane (60 ml) using phosphorus pentoxide (5.0g). Yield: (0.2g, 53%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.29 (s, 3H,  $\text{OCOCH}_3$ ), 5.18 (s, 2H, H2), 6.61-6.67 (m, 2H, ArH), 6.79 (bs, 1H, H4), 7.07 (d, 1H, J 7.9 Hz, H5), 7.23-7.45 (m, 5H, ArH).

25

## Example 31

### **4',7,8-Triacetoxydehydroequol (4',7,8-Triacetoxyisoflav-3-ene)**

Phosphorus pentoxide (5.0g) was added with stirring to a solution of *cis*- and *trans*-4',7,8-triacetoxyisoflavan-4-ol (0.5g, 1.3 mmol) in dry dichloromethane (50 ml). The mixture was 30 stirred at room temperature for 2h and filtered through a pad of Celite. The resulting solution was concentrated and chromatographed on silica gel to yield 4',7,8-triacetoxyisoflav-3-ene (0.3g, 63%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.29, 2.31, 2.32, (each s, 3H,

OCOCH<sub>3</sub>), 5.15 (s, 2H, H2), 6.72 (d, 1H, J 8.3 Hz, H6), 6.75 (bs, 1H, H4), 6.97 (d, 1H, J 7.9 Hz, H5), 7.12 (d, 2H, J 8.7 Hz ArH), 7.41 (d, 2H, J 8.7 Hz, ArH).

### Example 32

#### 5 7,8-Diacetoxy-4-methoxydehydroequol (7,8-Diacetoxy-4-methoxyisoflav-3-ene)

7,8-Diacetoxy-4-methoxyisoflav-3-ene was prepared from *cis*- and *trans*-7,8-diacetoxy-4-methoxyisoflavan-4-ol (0.4g, 1.1 mmol) in dry dichloromethane (60 ml) using phosphorus pentoxide (5.0g). Yield: (0.18g, 47%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.29, 2.32 (each s, 3H, OCOCH<sub>3</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 5.14 (s, 2H, H2), 6.69 (bs, 1H, H4), 6.71 (d, 1H, J 8.3 Hz, 10 H6), 6.90 (d, 2H, J 8.6 Hz ArH), 6.95 (d, 1H, J 7.9 Hz, H5), 7.36 (d, 2H, J 8.6 Hz, ArH).

### Example 33

#### 4',7-Diacetoxy-8-methylisoflav-3-ene

Phosphorus pentoxide (3.0g) was added with stirring to a solution of *cis*- and *trans*-4',7-15 diacetoxy-8-methylisoflavan-4-ol (0.55g, 1.5 mmol) in dry dichloromethane (25 ml). The mixture was stirred at room temperature for 2h and filtered through a pad of Celite. The resulting solution was concentrated and chromatographed on silica gel to yield 4',7-diacetoxy-8-methylisoflav-3-ene (0.25g, 48%). m.p. 140°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.04 (s, 3H, CH<sub>3</sub>), 2.31, 2.32 (each s, 3H, OCOCH<sub>3</sub>), 5.16 (s, 2H, H2), 6.61 (d, 1H, J 8.3 Hz, H6), 20 6.75 (bs, 1H, H4), 6.94 (d, 1H, J 8.3 Hz, H5), 7.13 (d, 2H, J 8.7 Hz, ArH), 7.45 (d, 2H, J 8.7 Hz, ArH). Mass spectrum: m/z 339 (M+1, 6%); 338 (M, 26); 296 (48); 254 (90); 253 (100).

### Example 34

#### 3',7-Diacetoxy-8-methylisoflav-3-ene

25 3',7-Diacetoxy-8-methylisoflav-3-ene was prepared from *cis*- and *trans*-3',7-diacetoxy-8-methylisoflavan-4-ol (0.25g, 0.7 mmol) in dry dichloromethane (20 ml) using phosphorus pentoxide (2.0g). Yield: (0.13g, 54%) m.p. 116°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.04 (s, 3H, CH<sub>3</sub>), 2.31, 2.32 (each s, 3H, OCOCH<sub>3</sub>), 5.16 (s, 2H, H2), 6.61 (d, 1H, J 8.3 Hz, H6), 6.79 (bs, 1H, H4), 6.92 (d, 1H, J 8.3 Hz, ArH), 7.05 (dd, 1H, J 2.0 Hz, 8.0 Hz, ArH), 7.15 (s, 1H, ArH), 30 7.26 (d, 1H, J 8.0 Hz, ArH), 7.37 (t, 1H, J 8.0 Hz, ArH). Mass spectrum: m/z 339 (M+1, 15%); 338 (M, 22); 296 (54); 254 (30).

**Example 35****7-Acet xy-4'-methoxy-8-methylisoflav-3-ene**

7-Acetoxy-4'-methoxy-8-methylisoflav-3-ene was prepared from *cis*- and *trans*-7-acetoxy-4'-methoxy-8-methylisoflavan-4-ol (0.25g, 0.7 mmol) in dry dichloromethane (20 ml) using phosphorus pentoxide (2.0g). Yield: (0.11g, 46%) m.p. 107°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.04 (s, 3H,  $\text{CH}_3$ ), 2.31 (s, 3H,  $\text{OCOCH}_3$ ), 3.83 (s, 3H, OMe), 5.16 (s, 2H, H2), 6.59 (d, 1H, J 8.3 Hz, H6), 6.68 (bs, 1H, H4), 6.90 (d, 1H, J 8.3 Hz, H5), 6.93 (d, 2H, J 9.0 Hz, ArH), 7.37 (d, 2H, J 9.0 Hz, ArH). Mass spectrum: m/z 311 (M+1, 13%); 310 (M, 68); 267 (100); 152 (68); 135 (90).

10

**Example 36****4',7-Diacetoxy-3'-methoxy-8-methylisoflav-3-ene**

4',7-Diacetoxy-3'-methoxy-8-methylisoflav-3-ene was prepared from *cis*- and *trans*-4',7-diacetoxy-3'-methoxy-8-methylisoflavan-4-ol (0.25g, 0.6 mmol) in dry dichloromethane (25 ml) using phosphorus pentoxide (2.0g). Yield: (0.14g, 58%) m.p. 123°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.05 (s, 3H,  $\text{CH}_3$ ), 2.31, 2.32 (each s, 3H,  $\text{OCOCH}_3$ ), 3.88 (s, 3H, OMe), 5.16 (s, 2H, H2), 6.61 (d, 1H, J 8.3 Hz, H6), 6.73 (bs, 1H, H4), 6.94 (d, 1H, J 8.3 Hz, H5), 6.97 (dd, 1H, J 1.9 Hz, 8.3 Hz, ArH), 7.03 (d, 1H, J 1.9 Hz, ArH), 7.05 (d, 1H, J 7.9 Hz, ArH).

20 **Deprotection Reactions****Example 37****Dehydroequol (Isoflav-3-ene-4',7-diol)**

Imidazole (0.09 g) was added to a suspension of 4',7-diacetoxydehydroequol (0.03 g, 0.09 mmol) in absolute ethanol (2.0 ml) and the mixture was refluxed for 45 min under argon. The solution was concentrated under reduced pressure and the product was precipitated by addition of distilled water (10 ml). The mixture was left overnight in the fridge and filtered to yield dehydroequol. The crude product was reprecipitated from methanol by addition of benzene to yield dehydroequol as fluffy white solid (0.012 g, 55%).  $^1\text{H}$  NMR ( $\text{CDCl}_3 + \text{d}_6\text{-DMSO}$ ):  $\delta$  4.93 (s, 2H, H2), 6.26 (bs, 1H, H4), 6.29 (dd, 1H, J 2.0 Hz, 8.2 Hz, H6), 6.50 (bs, 1H, H8), 6.73 (d, 2H, J 8.2 Hz, ArH), 6.76 (d, 2H, J 8.2 Hz, H5), 7.13 (d, 2H, J 8.2 Hz, ArH).

**Example 38****7-Hydroxy-4'-methoxyisoflav-3-ene**

Imidazole (0.18g) was added to a suspension of 7-acetoxy-4'-methoxyisoflav-3-ene (0.06g, 0.02 mmol) in absolute ethanol (5.0 ml) and the mixture was refluxed for 45 minutes under argon. The solution was concentrated under reduced pressure and the product was precipitated by addition of distilled water (10 ml). The mixture was left overnight in the fridge and filtered to yield isoflav-3-ene. The crude product was recrystallised from methanol/benzene to yield 7-hydroxy-4'-methoxyisoflav-3-ene (0.034g, 66%). <sup>1</sup>H NMR (CDCl<sub>3</sub> + d<sub>6</sub>-DMSO): δ 3.74 (s, 3H, OCH<sub>3</sub>), 4.99 (s, 2H, H2), 6.21 (d, 1H, J 2.3 Hz, H8), 6.29 (dd, 1H, J 2.3 Hz, 8.3 Hz, H6), 6.67 (bs, 1H, H4), 6.85 (d, 1H, J 8.3 Hz, H5), 6.86 (d, 2H, J 8.7 Hz, ArH), 7.33 (d, 2H, J 8.7 Hz, ArH).

**Example 39****15 Isoflav-3-ene-3',7-diol**

Isoflav-3-ene-3',7-diol was prepared from 3',7-diacetoxyisoflav-3-ene (0.09g, 0.3 mmol) and imidazole (0.3g) in ethanol (2.0 ml) as described for isoflav-3-ene-4',7-diol. Yield: (0.04g, 60%). <sup>1</sup>H NMR (CDCl<sub>3</sub> + d<sub>6</sub>-DMSO): δ 4.94 (s, 2H, H2), 6.21 (d, 1H, J 2.0 Hz, H8), 6.29 (dd, 1H, J 2.3 Hz, 8.3 Hz, H6), 6.62 (m, 1H, ArH), 6.64 (bs, 1H, H4), 6.75-6.82 (m, 3H, ArH), 7.07 (t, 1H, J 7.9 Hz, ArH), 8.99-9.17 (bs, 2H, OH).

**Example 40****3'-MethoxyIsoflav-3-ene-7-ol**

3'-MethoxyIsoflav-3-ene-7-ol was prepared from 7-acetoxy-3'-methoxyisoflav-3-ene (0.1g, 0.3 mmol) and imidazole (0.15g) in ethanol (2.0 ml) as described for isoflav-3-ene-4',7-diol. Yield: (0.06g, 70%) m.p. 75°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.84 (s, 3H, OMe), 5.12 (s, 2H, H2), 6.38 (d, 1H, J 2.0 Hz, H8), 6.40 (dd, 1H, J 2.0 Hz, 8.3 Hz, H6), 6.76 (bs, 1H, H4), 6.84 (dd, 1H, J 1.9 Hz, 8.3 Hz, ArH), 6.95 (m, 3H, ArH), 7.29 (t, 1H, J 8.3 Hz, ArH).

**30 Example 41****3'-MethoxyIsoflav-3-ene-4',7-diol**

3'-MethoxyIsoflav-3-ene-4',7-diol was prepared from 4',7-diacetoxy-3-methoxyisoflav-3-ene (0.11g, 0.3 mmol) and imidazole (0.3g) in ethanol (2.0 ml) as described for isoflav-3-ene-4',7-diol. Yield: (0.06g, 71%).  $^1\text{H}$  NMR ( $d_6$ -acetone):  $\delta$  3.90 (s, 3H, OMe), 5.07 (s, 2H, H2), 6.31 (d, 1H, J 2.3 Hz, H8), 6.40 (dd, 1H, J 2.3 Hz, 8.3 Hz, H6), 6.78 (bs, 1H, H4), 6.83 5 (d, 1H, J 8.3 Hz, ArH), 6.92 (dd, 2H, J 1.9 Hz, 8.3 Hz, ArH), 7.14 (d, 1H, J 1.9 Hz, ArH), 7.04,7.63 (each s, 1H, OH).

#### Example 42

##### Isوفлав-3-ене-7-ол

10 Isoflav-3-ene-7-ol was prepared from 7-acetoxyisoflav-3-ene (0.2g, 0.75 mmol) and imidazole (0.24g) in ethanol (3.5 ml) as described for isoflav-3-ene-4',7-diol. Yield: (0.11g, 66%) m.p. 120°C.  $^1\text{H}$  NMR ( $d_6$ -DMSO):  $\delta$  5.07 (s, 2H, H2), 6.24 (d, 1H, J 2.2 Hz, H8), 6.33 (dd, 1H, J 1.9 Hz, 7.9 Hz, H6), 6.96 (d, 1H, J 7.9 Hz, H5), 7.00 (s, 1H, H4), 7.26-7.47 (m, 5H, ArH), 9.65 (bs, 1H, OH). Mass spectrum: m/z 224 (m, 74%); 223 (100), 175 (28); 15 165 (23); 147 (41).

#### Example 43

##### Isофлав-3-ене-4',7,8-триол

Imidazole (0.6g) was added to a suspension of 4',7,8-triacetoxyisoflav-3-ene (0.16g, 0.4 mmol) in absolute ethanol (5.0 ml) and the mixture was refluxed for 45 min under argon. The solution was concentrated under reduced pressure and the product was precipitated by addition of distilled water (10 ml). The mixture was left overnight in the fridge and filtered to yield isoflav-3-ene. The crude product was recrystallised from methanol/benzene to yield Isoflav-3-ene-4',7,8-triol (0.08g, 75%).  $^1\text{H}$  NMR ( $\text{CDCl}_3 + d_6$ -DMSO):  $\delta$  4.97 (s, 2H, H2), 6.30 (d, 1H, J 8.2 Hz, H6), 6.36 (d, 1H, J 8.3 Hz, H5), 6.55 (bs, 1H, H4), 6.72 (d, 1H, J 8.7 Hz, ArH), 7.17 (d, 2H, J 8.7 Hz, ArH).

#### Example 44

##### 4'-Метоксиисофлав-3-ене-7,8-диол

30 4'-Метоксиисофлав-3-ене-7,8-диол was prepared from 7,8-diacetoxy-4-methoxyisoflav-3-ene (0.15g, 0.4 mmol) and imidazole (0.4g) in ethanol (1.6 ml) as described for isoflav-3-ene-4',7,8-triol. Yield: (0.73g, 61%).  $^1\text{H}$  NMR ( $\text{CDCl}_3 + d_6$ -DMSO):  $\delta$  3.83 (s, 3H, OCH<sub>3</sub>),

5.15 (s, 2H, H2), 6.51 (d, 1H, J 8.3 Hz, H6), 6.58 (d, 1H, J 8.3 Hz, H5), 6.68 (bs, 1H, H4), 6.92 (d, 1H, J 8.7 Hz, ArH), 7.35 (d, 2H, J 8.7 Hz, ArH). Mass spectrum: m/z 270 (M, 5%); 256 (100); 255 (70); 239 (20); 181 (25).

## 5 Example 45

### **8-Methylisoflav-3-ene-4',7-diol**

Imidazole (0.6g) was added to a suspension of 4',7-diacetoxy-8-methylisoflav-3-ene (0.25g, 0.7 mmol) in absolute ethanol (5.0 ml) and the mixture was refluxed for 45 min under argon. The solution was concentrated under reduced pressure and the product was precipitated by 10 addition of distilled water (10 ml). The mixture was left overnight in the fridge and filtered to yield isoflav-3-ene. The crude product was recrystallised from methanol/benzene to yield 8-methylisoflav-3-ene-4',7-diol (0.13g, 68%). m.p. 190-93°C <sup>1</sup>H NMR (CDCl<sub>3</sub> + d<sub>6</sub>-DMSO): δ 1.94 (s, 3H, CH<sub>3</sub>), 4.98 (s, 2H, H2), 6.32 (d, 1H, J 7.9 Hz, H6), 6.58 (bs, 1H, H4), 6.67 (bd, 1H, H5), 6.72 (d, 2H, J 8.7 Hz, ArH), 7.21 (bd, 2H, ArH). Mass spectrum: 15 m/z 255 (M+1, 16%); 254 (M, 79); 253 (100); 161 (32).

## **Example 46**

### **8-Methylisoflav-3-ene-3',7-diol**

8-Methylisoflav-3-ene-3',7-diol was prepared from 3',7-diacetoxy-8-methylisoflav-3-ene 20 (0.12g, 0.4 mmol) and imidazole (0.3g) in ethanol (2.5 ml) as described for 8-methylisoflav-3-ene-4',7-diol. Yield: (0.07g, 77%) m.p. 130°C. <sup>1</sup>H NMR (CDCl<sub>3</sub> + d<sub>6</sub>-DMSO): δ 1.95 (s, 3H, CH<sub>3</sub>), 4.98 (s, 2H, H2), 6.34 (d, 1H, J 8.0 Hz, H6), 6.61-6.94 (m, 5H, ArH), 7.08 (bt, 1H, ArH). Mass spectrum: m/z 254 (M, 100%); 253 (96); 161 (45).

## 25 Example 47

### **4'-Methoxy-8-methylisoflav-3-ene-7-ol**

4'-Methoxy-8-methylisoflav-3-ene-7-ol was prepared from 7-acetoxy-4'-methoxy-8-methylisoflav-3-ene (0.11g, 0.3 mmol) and imidazole (0.14g) in ethanol (1.5 ml) as described for 8-methylisoflav-3-ene-4',7-diol. Yield: (0.05g, 53%) m.p. 103°C. <sup>1</sup>H NMR 30 (d<sub>6</sub>-acetone): δ 1.99 (s, 3H, CH<sub>3</sub>), 3.81 (s, 3H, OMe), 5.11 (s, 2H, H2), 6.43 (d, 1H, J 8.3 Hz, H6), 6.77 (bs, 1H, H4), 6.80 (d, 1H, J 8.3 Hz, H5), 6.95 (d, 2H, J 9.0 Hz, ArH), 7.44 (d, 2H, J 9.0 Hz, ArH). Mass spectrum: 282 (M, 9%); 267 (100); 268 (95); 134 (52).

**Example 48****3'-Methoxy-8-methylisoflav-3-ene-4',7-diol**

3'-Methoxy-8-methylisoflav-3-ene-4',7-diol was prepared from 4',7-diacetoxy-3'-methoxy-8-methylisoflav-3-ene (0.21g, 0.6 mmol) and imidazole (0.52g) in ethanol (4 ml) as described for 8-methylisoflav-3-ene-4',7-diol. Yield: (0.1g, 63%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.14 (s, 3H,  $\text{CH}_3$ ), 3.94 (s, 3H, OMe), 5.11 (s, 2H, H2), 6.42 (d, 1H, J 8.3 Hz, H6), 6.64 (bs, 1H, ArH), 6.80 (d, 1H, J 7.9 Hz, ArH), 6.94 (m, 2H, ArH), 7.12 (m, 1H, ArH), 7.26, 7.70 (each bs, 1H, OH).

10

**Deprotection Reactions****Example 49****cis- and trans-Tetrahydrodaidzein**

15 Imidazole (0.2 g) was added to a suspension of 4',7-diacetoxytetrahydrodaidzein (0.10 g, 0.3 mmol) in absolute ethanol (4.0 ml) and the mixture refluxed for 45 min under argon. The solution was concentrated under reduced pressure and distilled water (10 ml) was added. The mixture was left overnight in the fridge and the crystalline product was filtered to yield cis- and trans-tetrahydrodaidzein (0.06 g, 80%).

20

**Example 50*****trans*-Tetrahydrodaidzein (*trans*-4',7-Dihydroxyisoflavan-4-ol)**

Trans-4',7-dihydroxyisoflavan-4-ol was prepared from *trans*-4',7-dihydroxyisoflavan-4-ol and imidazole in ethanol as described for cis- and *trans*-tetrahydrodaidzein.  $^1\text{H}$  NMR ( $d_6$ -acetone):  $\delta$  2.99 (ddd, 1H, J 3.4 Hz, 6.8 Hz, 10.6 Hz, H3), 4.13 (dd, 1H, J 7.0 Hz, 10.9 Hz, H2); 4.24 (dd, 1H, J 3.8 Hz, 11.3 Hz, H2), 4.70 (d, 1H, J 6.4 Hz, H4), 6.20 (d, 1H, J 2.6 Hz, H8), 6.38 (dd, 1H, J 2.3 Hz, 8.3 Hz, H6), 6.71 (d, 2H, J 8.7 Hz, ArH), 7.04 (d, 2H, J 8.7 Hz, ArH), 7.18 (d, 1H, J 8.3 Hz, H5).

30 Example 51

***cis*- and *trans*-7-Hydroxy-4'-methoxyisoflavan-4-ol**

Imidazole (0.4 g) was added to a suspension of 7-acetoxy-4'-methoxyisoflavan-4-ol (0.20 g, 0.6 mmol) in absolute ethanol (8.0 ml) and the mixture refluxed for 45 minutes under argon. The solution was concentrated under reduced pressure and distilled water (10 ml) was added. The mixture was left overnight in the fridge and the crystalline product was filtered 5 to yield *cis*- and *trans*-7-hydroxy-4'-methoxyisoflavan-4-ol (0.16g, 79%).

**Example 52**

***cis*- and *trans*-7-Hydroxyisoflavan-4-ol**

7-hydroxyisoflavan-4-ol was prepared from 7-acetoxyisoflavan-4-ol (0.14g, 0.5 mmol) and 10 Imidazole (0.17g) in ethanol (3.0 ml) as described for *cis*- and *trans*-tetrahydrodaidzein.

For *trans*-7-hydroxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{d}_6$ -acetone):  $\delta$  3.08 (m, 1H, H3), 4.00 (t, 1H, J 10.2 Hz, H2); 4.30 (m, 1H, H2), 4.81 (d, 1H, J 7.2 Hz, H4), 6.25-6.43 (m, ArH), 6.89 (d, J 8.3 Hz, ArH), 7.07 (d, J 8.3 Hz, ArH), 7.22-7.64 (m, ArH).

15

For *cis*-7-acetoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{d}_6$ -acetone):  $\delta$  3.20 (m, 1H, H3), 4.36 (m, 1H, H2); 4.57 (dd, 1H, J 10.2 Hz, 12.0 Hz, H2), 4.68 (bs, 1H, H4), 6.25-6.43 (m, ArH), 6.89 (d, J 8.3 Hz, ArH), 7.07 (d, J 8.3 Hz, ArH), 7.22-7.64 (m, ArH).

20 **Example 53**

***cis*- and *trans*-4',7-Dihydroxy-8-methylisoflavan-4-ol**

4',7-Dihydroxy-8-methylisoflavan-4-ol was prepared from 4',7-diacetoxy-8-methylisoflavan-4-ol (0.4g, 1.1 mmol) and imidazole (1.0g) in ethanol (7.0 ml) as described for *cis*- and *trans*-tetrahydrodaidzein.

25

For *trans*-4',7-dihydroxy-8-methylisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{d}_6$ -acetone):  $\delta$  1.98 (s, 3H,  $\text{CH}_3$ ), 2.98 (ddd, 1H, J 3.8 Hz, 10.9 Hz, 12.0 Hz, H3), 4.18 (m, 1H, H2); 4.27 (m, 1H, H2), 4.75 (d, 1H, J 6.4 Hz, H4), 6.42 (m, ArH), 6.75 (m, ArH), 7.05-7.19 (m, ArH), 7.66 (bs, OH).

30

For *cis*-4',7-dihydroxy-8-methylisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{d}_6$ -acetone):  $\delta$  1.99 (s, 3H,  $\text{CH}_3$ ), 3.01 (dt, 1H,  $J$  3.4 Hz, 12.0 Hz, H3), 4.31 (m, 1H, H2); 4.52 (dd, 1H,  $J$  10.2 Hz, 12.0 Hz, H2), 4.60 (bs, 1H, H4), 6.42 (m, ArH), 6.75 (m, ArH), 7.05-7.19 (m, ArH), 7.66 (bs, OH).

## 5 Example 54

### *trans*-7-Hydroxy-4'-methoxy-8-methylisoflavan-4-ol

*trans*-7-Hydroxy-4'-methoxy-8-methylisoflavan-4-ol was prepared from *trans*-7-acetoxy-4'-methoxy-8-methylisoflavan-4-ol (0.23g, 0.7 mmol) and imidazole (0.28g) in ethanol (2.1 ml) as described for *cis*- and *trans*-tetrahydrodaidzein. m.p. 162°C. Mass spectrum: 285 M, 10 5%); 268 (10); 151 (20); 135 (20); 134 (100); 119 (20).  $^1\text{H}$  NMR ( $\text{d}_6$ -acetone):  $\delta$  1.97 (s, 3H,  $\text{CH}_3$ ), 3.00 (ddd, 1H,  $J$  3.4 Hz, 7.2 Hz, 10.2 Hz, H3), 3.72 (s, 3H, OMe), 4.20 (dd, 1H,  $J$  7.5 Hz, 10.9 Hz, H2); 4.27 (m, 1H, H2), 4.73 (d, 1H,  $J$  6.8 Hz, H4), 6.45 (d, 1H,  $J$  8.3 Hz, H6), 6.85 (d, 2H,  $J$  8.6 Hz, ArH), 7.10 (d, 1H,  $J$  8.7 Hz, H5), 7.18 (d, 2H,  $J$  8.6 Hz, ArH).

## 15 Hydrogenation Reactions:- Isoflavone → cis-Isoflavan-4-ol

### Example 55

#### *cis*-4',7-Diacetoxyisoflavan-4-ol

Platinum(IV)oxide (Adam's catalyst) (0.05g) was added to a solution of 4',7-diacetoxyisoflavanone (0.25g, 0.7 mmol) in ethyl acetate (40 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 55h. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield predominantly the *cis*-4',7-diacetoxyisoflavan-4-ol.

25 For *cis*-4',7-diacetoxyisoflavan-4-ol;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.28 (s, 3H,  $\text{OCOCH}_3$ ), 2.29 (s, 3H,  $\text{OCOCH}_3$ ), 3.30 (dt, 1H,  $J$  3.4 Hz,  $J$  11.8 Hz, H3), 4.31 (ddd, 1H,  $J$  1.4 Hz, 3.6 Hz, 10.5 Hz, H2); 4.56 (dd, 1H,  $J$  10.5 Hz, 11.8 Hz, H2), 4.75 (dd, 1H,  $J$  1.3 Hz, 3.2 Hz, H4), 6.66 (dd, 1H,  $J$  2.3 Hz, 8.7 Hz, H6), 6.69 (d, 1H,  $J$  2.3 Hz, H8), 7.08 (d, 2H,  $J$  8.6 Hz, ArH), 7.26 (d, 1H, 8.4 Hz, H5), 7.29 (d, 2H,  $J$  8.6 Hz, ArH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  20.98 ( $\text{OCOCH}_3$ ), 30 43.52 (C3), 64.10 (C2), 66.46 (C4), 110.08 (C6), 114.09 (C8), 121.82, 129.40 (ArCH), 131.10 (C5).

**Hydrogenation Reactions:- Isoflavone → Isoflavan-4-one****Example 56****4',7-Diacetoxydihydrodaidzein (4',7-Diacetoxyisoflavan-4-one)**

5 Palladium-on-charcoal (5%, 0.02g) was added to a solution of 4',7-diacetoxydaidzein (0.50g, 1.5 mmol) in ethyl acetate (80 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 72h. The catalyst was removed by filtration through Celite and the resulting filtrate was evaporated *in vacuo*. The residue was recrystallised from ethanol to yield 4',7-diacetoxydihydrodaidzein (0.40g, 80%) as colourless plates. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 10 δ 2.29 (s, 3H, OCOCH<sub>3</sub>), 2.23 (s, 3H, OCOCH<sub>3</sub>), 3.98 (dd, 1H, J 6.2 Hz, 8.2 Hz, H3), 4.69 (m, 2H, H2), 6.78-6.82 (m, 2H, ArH), 7.08 (d, 2H, J 9.2 Hz, ArH), 7.30 (d, 2H, J 8.2 Hz, ArH), 7.98 (d, 1H, J 9.2 Hz H5).

**Hydrogenation Reactions:- Isoflavan-3-ene → Isoflavan**

15

**Example 57****O,O-Diacetylequol**

Palladium-on-charcoal (5%, 0.02g) was added to a solution of 4',7-diacetoxyisoflavan-3-ene (0.20g, 0.06 ml) in ethyl acetate (60 ml) and the mixture was stirred at room temperature 20 under a hydrogen atmosphere for 24h. The catalyst was removed by filtration through Celite and the resulting filtrate was evaporated *in vacuo*. The residue was recrystallised from dichloromethane/light petroleum to yield O,O-diacetylequol (0.15g, 75%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.29 (s, 3H, OCOCH<sub>3</sub>), 2.31 (s, 3H, OCOCH<sub>3</sub>), 3.00 (d, 2H, J 8.3 Hz, H4), 3.25 (m, 1H, H3), 4.00 (t, 1H, H2), 4.34 (dd, 1H, J 3.4 Hz, 10.9 Hz, H2), 6.61 (d, J 7.5 Hz, 1H, 25 ArH), 6.60 (s, 1H, ArH), 7.06 (bd, 3H, J 8.3 Hz, ArH), 7.24 (d, 3H, J 8.3 Hz, ArH).

**Deprotection Reactions**30 **Example 58****Dihydridaidzein (4',7-Dihydridoxyisoflavan-4-one)**

Imidazole (0.63g) was added to a suspension of 4',7-diacetoxydihydrodaidzein (0.26g, 0.08 mmol) in absolute ethanol (5.0 ml) and the mixture was refluxed for 45 min under argon.

The solution was concentrated under reduced pressure and distilled water (10 ml) was added to the residue. The mixture was left overnight in the fridge and the resulting precipitate was filtered. The crude product was recrystallised from ethyl acetate/dichloromethane to yield 4',7-diacetoxymethyldihydrodaidzein (0.14g, 71%) as a white powder. <sup>1</sup>H NMR (d<sub>6</sub>-acetone): δ 5 3.83 (t, 1H, J 7.2 Hz, H3), 4.60 (d, 2H, J 6.2 Hz, H2), 6.39 (d, 1H, J 2.0 Hz, H8), 6.55 (dd, 1H, J 8.2, J 2.0 Hz, ArH), 6.80 (d, 2H, J 8.2 Hz, ArH), 7.10 (d, 1H, J 8.2 Hz, ArH), 7.74 (d, 1H, J 8.2 Hz, H5).

### Example 59

#### 10 Equol (4',7-Dihydroxyisoflavan)

Imidazole 0.5g) was added to a suspension of C<sub>3</sub>O-diacetylequol (0.15g, 0.08 mmol) in absolute ethanol (5.0 ml) and the mixture was refluxed for 45 min under argon. The solution was concentrated under reduced pressure and distilled water (10 ml) was added to the residue. The mixture was left overnight in the fridge and the resulting product was 15 filtered to yield equol (0.09g, 80%) as a white powder. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO): δ 2.70 (d, 2H, J 9.2 Hz, H4), 2.92 (m, 1H, H3), 3.73 (t, 1H, J 10.3 Hz, H2), 4.06 (dd, 1H, J 3.0 Hz, 11.2 Hz, H2), 6.16 (bs, 1H, ArH), 6.21 (bd, J 8.2 Hz, 1H, ArH), 6.63 (d, 2H, J 8.2 Hz, ArH), 6.69 (d, 1H, J 8.2 Hz, ArH), 6.87 (d, 2H, J 8.2 Hz, ArH)

20

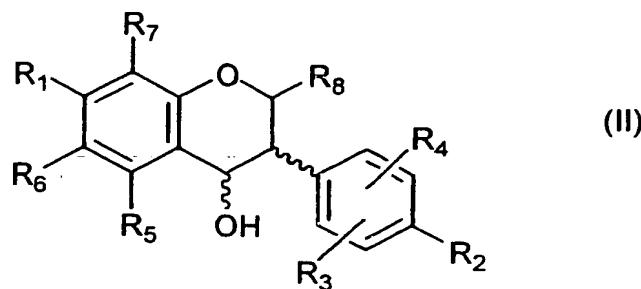
Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The inventions also includes all of the steps, features, compositions and compounds referred to or indicated in 25 the specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

The claims defining the invention are as follows:

1. A method for the preparation of a compound of formula II

5

10



wherein

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>,

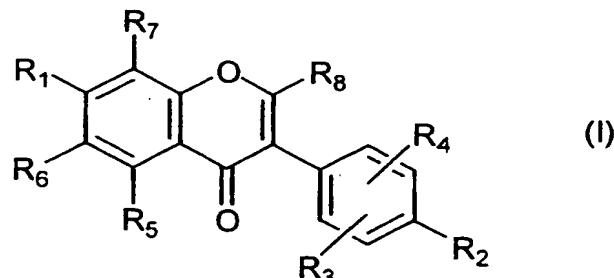
15 OS(O)R<sub>9</sub>, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro, or halo, and

R<sub>9</sub> is alkyl, haloalkyl, aryl, arylalkyl or alkylaryl,

comprising the step of hydrogenating a compound of formula I

20

25



wherein

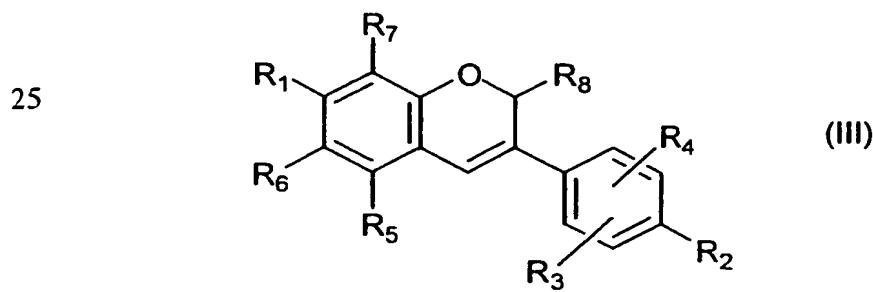
R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are as defined above

to prepare a compound of formula II.

30

2. A method of claim 1, wherein the hydrogenation step is performed with hydrogen in the presence of a reduction catalyst and a solvent.

3. A method of claim 2, wherein the reduction catalyst comprises palladium, palladium hydroxide, platinum or platinum oxide.
4. A method of claim 3, wherein the reduction catalyst is palladium on activated carbon, 5 palladium on barium sulfate or platinum(IV)oxide.
5. A method of claim 4, wherein the reduction catalyst is palladium on activated carbon (1% Pd to 10% Pd).
- 10 6. A method of claim 5, wherein the reduction catalyst is about 5% palladium on activated carbon.
7. A method of claim 2, wherein the solvent is a C<sub>1</sub>-C<sub>8</sub> alcohol, an alkyl acetate or a C<sub>1</sub>-C<sub>3</sub> carboxylic acid.
- 15 8. A method of claim 7, wherein the solvent is a methanol, ethanol or C<sub>1</sub>-C<sub>6</sub> alkyl acetate.
9. A method of claim 8, wherein the solvent is absolute methanol or absolute ethanol.
- 20 10. A method of claim 1 which further comprises the step of dehydrating and optionally deprotecting or transforming a compound of formula II to prepare a compound of formula III



30

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, OS(O)R<sub>9</sub>, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro, or halo, and

R<sub>9</sub> is alkyl, haloalkyl, aryl, arylalkyl or alkylaryl.

11. A method of any one of claims 1 to 10, wherein the compounds of formula I, II or III have the following substituents

5 R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or arylalkyl,

R<sub>8</sub> is hydrogen, and

R<sub>9</sub> is methyl, ethyl, propyl, isopropyl or trifluoromethyl.

10

12. A method of claim 11, wherein the compounds of formula I, II or III have the following substituents

R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>7</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or 15 arylalkyl,

R<sub>6</sub> and R<sub>8</sub> are hydrogen, and

R<sub>9</sub> is methyl.

13. A method of any one of claims 1 to 12, wherein the compound of formula I is 4',7-

20 diacetoxyisoflavone (daidzein diacetate) or 7-acetoxy-4'-methoxyisoflavone.

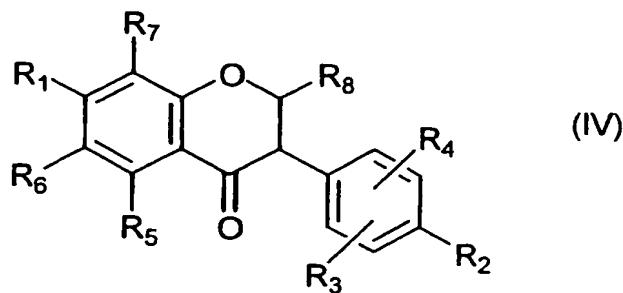
14. A method of any one of claims 1 to 13, wherein the compound of formula II is 4',7-diacetoxyisoflavan-4-ol (tetrahydrodaidzein diacetate) or 7-acetoxy-4'-methoxyisoflavan-4-ol.

25

15. A method of any one of claims 10 to 14, wherein the compound of formula III is 4',7-diacetoxyisoflav-3-ene (dehydroequol diacetate), 4',7-dihydroxyisoflav-3-ene (dehydroequol), 7-acetoxy-4'-methoxyisoflav-3-ene or 7-hydroxy-4'-methoxyisoflav-3-ene.

30 16. A method for the preparation of a compound of formula IV

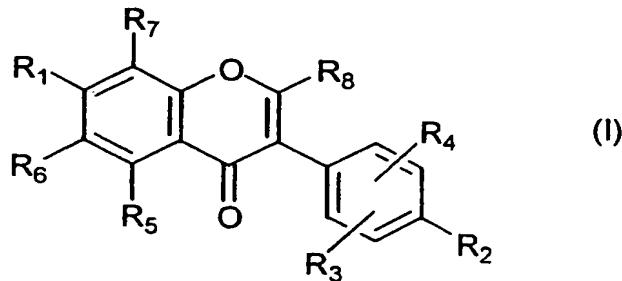
5

**wherein**

- 10 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, OS(O)R<sub>9</sub>, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro, or halo, and  
R<sub>9</sub> is alkyl, haloalkyl, aryl, arylalkyl or alkylaryl,  
comprising the step of hydrogenating a compound of formula I

15

20

**wherein**

- R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are as defined above  
25 to prepare a compound of formula IV.

17. A method of claim 16, wherein the hydrogenation step is performed with hydrogen in the presence of a reduction catalyst and a solvent.

30 18. A method of claim 17, wherein the reduction catalyst comprises palladium, palladium hydroxide, platinum or platinum(IV)oxide.

19. A method of claim 18, wherein the reduction catalyst is palladium on activated carbon (1% Pd to 10% Pd).

20. A method of claim 19, wherein the reduction catalyst is about 5% palladium on activated carbon.

21. A method of claim 17, wherein the solvent is a C<sub>1</sub>-C<sub>8</sub> alcohol, a C<sub>1</sub>-C<sub>6</sub> alkyl acetate or a C<sub>1</sub>-C<sub>3</sub> carboxylic acid.

10 22. A method of claim 21, wherein the solvent is absolute methanol, ethanol or ethyl acetate.

23. A method of any one of claims 16 to 22, wherein the compound of formula I is 4',7-diacetoxyisoflavone (daidzein diacetate) or 7-acetoxy-4'-methoxyisoflavone.

15

24. A method of any one of claims 16 to 22, wherein the compound of formula IV has the following substituents

R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or arylalkyl,

R<sub>8</sub> is hydrogen, and

R<sub>9</sub> is methyl, ethyl, propyl, isopropyl or trifluoromethyl.

25 25. A method of claim 24, wherein the compound of formula IV has the following substituents

R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>7</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or arylalkyl,

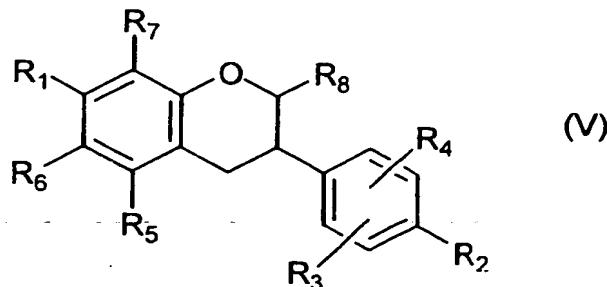
R<sub>6</sub> and R<sub>8</sub> are hydrogen, and

30 R<sub>9</sub> is methyl.

26. A method of claim 25, wherein the compound of formula IV is 4',7-diacetoxyisoflavan-4-one (diacetoxylidihydrodaidzein) or 4',7-dihydroxyisoflavan-4-one (dihydrodaidzein).

## 27. A method for the preparation of a compound of formula V

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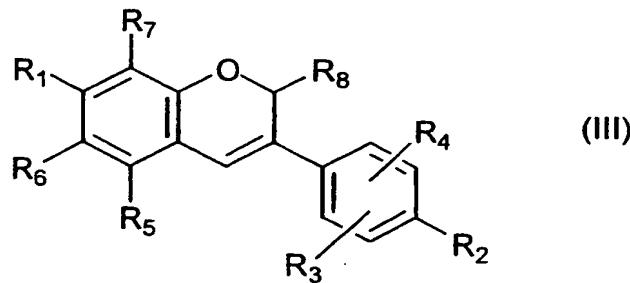
10

wherein

$R_1, R_2, R_3, R_4, R_5, R_6, R_7$  and  $R_8$  are independently hydrogen, hydroxy,  $OR_9$ ,  $OC(O)R_9$ ,  $OS(O)R_9$ , alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro, or halo, and

15  $R_9$  is alkyl, haloalkyl, aryl, arylalkyl or alkylaryl,  
comprising the step of hydrogenating a compound of formula III

20



25 wherein

$R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8$  and  $R_9$  are as defined above  
to prepare a compound of formula V.

28. A method of claim 27, wherein the hydrogenation step is performed with hydrogen in  
30 the presence of a reduction catalyst and a solvent.

29. A method of claim 28, wherein the reduction catalyst comprises palladium, palladium hydroxide, platinum or platinum(IV)oxide.

30. A method of claim 29, wherein the reduction catalyst is palladium on activated carbon (1% Pd to 10% Pd).
- 5 31. A method of claim 30, wherein the reduction catalyst is about 5% palladium on activated carbon.
32. A method of claim 28, wherein the solvent is a C<sub>1</sub>-C<sub>8</sub> alcohol, a C<sub>1</sub>-C<sub>6</sub> alkyl acetate or a C<sub>1</sub>-C<sub>3</sub> carboxylic acid.
- 10 33. A method of claim 32, wherein the solvent is a methanol, ethanol or ethyl acetate.
34. A method of claim 33, wherein the solvent is ethyl acetate.
- 15 35. A method of any one of claims 27 to 34, wherein and the compound of formula III is 4',7-diacetoxysflav-3-ene (dehydroequol diacetate), 4',7-dihydroxysflav-3-ene (dehydroequol), 7-acetoxy-4'-methoxysflav-3-ene or 7-hydroxy-4'-methoxysflav-3-ene.
36. A method of any one of claims 27 to 34, wherein the compound of formula V has the  
20 following substituents
- R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,
- R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or arylalkyl,
- R<sub>8</sub> is hydrogen, and
- 25 R<sub>9</sub> is methyl, ethyl, propyl, isopropyl or trifluoromethyl.
37. A method of claim 36, wherein the compound of formula V has the following substituents
- R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,
- 30 R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>7</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or arylalkyl,
- R<sub>6</sub> and R<sub>8</sub> are hydrogen, and
- R<sub>9</sub> is methyl.

38. A method of claim 37, wherein the compound of formula V is 4',7-diacetoxyisoflavan (equol diacetate) or 4',7-dihydroxyisoflavan (equol).
- 5 39. Methods substantially as hereinbefore described especially with reference to the Examples.
40. Compounds of formula II or formula III or formula IV or formula V when prepared by a method of any preceding claim.
- 10 41. A compound of the formula I, II, III, IV or V,  
wherein  
R<sub>1</sub> is hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, thio, alkylthio, or halo,  
R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are independently hydrogen, hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>,  
15 OS(O)R<sub>9</sub>, alkyl, aryl, thio, alkylthio or halo, and  
R<sub>9</sub> is alkyl, fluoroalkyl or arylalkyl  
with the proviso that  
at least one of R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> is not hydrogen, or  
when R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are all hydrogen, then R<sub>3</sub> is hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, OS(O)R<sub>9</sub>, alkyl,  
20 aryl, thio, alkylthio or halo.
42. A compound of claim 41,  
wherein  
R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,  
25 R<sub>2</sub> and R<sub>3</sub> are independently hydrogen, hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,  
R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are hydrogen,  
R<sub>7</sub> is hydroxy, OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or halo, and  
R<sub>9</sub> is methyl, ethyl, propyl, isopropyl, trifluoromethyl or benzyl.
- 30 43. A compound of claim 41,  
wherein  
R<sub>1</sub> is hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,  
R<sub>2</sub> and R<sub>3</sub> are independently hydrogen, hydroxy, OR<sub>9</sub> or OC(O)R<sub>9</sub>,

R<sub>5</sub> is OR<sub>9</sub>, OC(O)R<sub>9</sub>, alkyl, aryl or halo,  
R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub>, and R<sub>8</sub> are hydrogen, and  
R<sub>9</sub> is methyl, ethyl, propyl, isopropyl, trifluoromethyl or benzyl.

5 44. A compound of claim 41 selected from the group consisting of:

- 4',7,8-Triacetoxyisoflavone
- 7,8-Diacetoxy-4'-methoxyisoflavone
- 4',7-Diacetoxy-8-methylisoflavone
- 3',7-Diacetoxy-8-methylisoflavone
- 10 7-Acetoxy-4'-methoxy-8-methylisoflavone
- 4',7-Diacetoxy-3'-methoxy-8-methylisoflavone
- 4',5,7-Triacetoxyisoflavone
- 4',7,8-Triacetoxyisoflavan-4-ol
- 15 7,8-Diacetoxy-4-methoxyisoflavan-4-ol
- 4',7-Diacetoxy-8-methylisoflavan-4-ol
- 3',7-Diacetoxy-8-methylisoflavan-4-ol
- 7-Acetoxy-4'-methoxy-8-methylisoflavan-4-ol
- 4',7-Diacetoxy-3'-methoxy-8-methylisoflavan-4-ol
- 20 4',5,7-Triacetoxyisoflavan-4-ol
- 4',7,8-Trihydroxyisoflavan-4-ol
- 7,8-Dihydroxy-4-methoxyisoflavan-4-ol
- 4',7-Dihydroxy-8-methylisoflavan-4-ol
- 25 3',7-Dihydroxy-8-methylisoflavan-4-ol
- 7-Hydroxy-4'-methoxy-8-methylisoflavan-4-ol
- 4',7-Dihydroxy-3'-methoxy-8-methylisoflavan-4-ol
- 4',5,7-Trihydroxyisoflavan-4-ol
- 30 4',7,8-Triacetoxydehydroequol (4',7,8-Triacetoxyisoflav-3-ene)
- 7,8-Diacetoxy-4-methoxydehydroequol (7,8-Diacetoxy-4-methoxyisoflav-3-ene)
- 4',7-Diacetoxy-8-methylisoflav-3-ene
- 3',7-Diacetoxy-8-methylisoflav-3-ene

- 48 -

7-Acetoxy-4'-methoxy-8-methylisoflav-3-ene

4',7-Diacetoxy-3'-methoxy-8-methylisoflav-3-ene

4',5,7-Triacetoxyisoflav-3-ene

5 Isoflav-3-ene-4',7,8-triol

4'-Methoxyisoflav-3-ene-7,8-diol

8-Methylisoflav-3-ene-4',7-diol

8-Methylisoflav-3-ene-3',7-diol

4'-Methoxy-8-methylisoflav-3-ene-7-ol

10 3'-Methoxy-8-methylisoflav-3-ene-4',7-diol

Isoflav-3-ene-4',5,7-triol

4',7-Dihydroxy-8-methylisoflavan-4-ol

7-Hydroxy-4'-methoxy-8-methylisoflavan-4-ol

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU 00/00103

**A. CLASSIFICATION OF SUBJECT MATTER**Int Cl<sup>7</sup>: C07D 311/36, 311/38, 311/04, 311/56

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
STN: sub-structure search**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU 80655/87 (606087) B (ZYMA S A) 5 May 1988 Page 16, lines 4-8	1-9
X	Page 12, lines 13-19	16-17
X	Page 10, part (b)	27-28
X	Formula I, page 1 (relates to instant formula V), Formula II, page 10 (form I, IV), Formula III, page 10 (form III), Formula IIa, page 14 (form I), Formula IIc, page 16 (form II)	41-44

 Further documents are listed in the continuation of Box C See patent family annex

## \* Special categories of cited documents:

- "A" Document defining the general state of the art which is not considered to be of particular relevance  
 "E" earlier application or patent but published on or after the international filing date  
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 "O" document referring to an oral disclosure, use, exhibition or other means  
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art  
 "&" document member of the same patent family

Date of the actual completion of the international search

21 March 2000

Date of mailing of the international search report

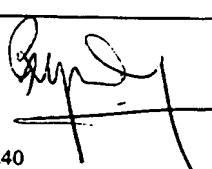
24 MAR 2000

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/AU 00/00103

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Tetrahedron Letters, Volume 21, 1972 (UK), L Jurd et al, "Phenolic and Quinoidal Constituents of Dalbergia Retusa", pages 2149-2152 Formulas I and II (relates to instant formula I)	41-43
X	Formula I on page 2150, lines 3, 4 gives 7,8 Diacetoxy-4 <sup>1</sup> -methoxyisoflavone (4H-1-Benzopyran-4-one, 7,8-bis (acetyloxy)-3-(4-methoxyphenyl)-) (see instant page 47, line 7)	44
X	Journal of the Chemical Society 1957 (UK), W B Whalley, "5,4 <sup>1</sup> -Dihydroxy-8-methyl isoflavone, and a Note on Lotoflavin" pages 1833-1837 Formulas I and II (relates to instant formula I, IV). See page 1834, lines 7, 9, 27, 29, 30	41-43
X	Phytochemistry, Volume 28, No: 9, 1989 (UK), L V Alegrio et al, "Diarylheptanoids and Isoflavonoids from Centrolobium Species", pages 2359-2362 Formulas IV-VII (relates to instant formulas V, I, IV, III, respectively). See page 2360	41-43
X	Patent Abstracts of Japan, JP 10-059956 A (KIKKOMAN CORPORATION) 3 March 1998 See formula I (relates to instant formula I)	41-43
X	Patent Abstracts of Japan, JP 6-321752 A (KAO CORPORATION) 22 November 1994 See formula (relates to instant formula I)	41-44
X	Patent Abstracts of Japan, JP 6-086682 A (KOBE STEEL LTD) 29 March 1994 See 4 <sup>1</sup> ,7,8-trihydroxyisoflavone (relates to instant formula I)	41-43
X	Patent Abstracts of Japan, JP 6-040876 A (KOBE STEEL LTD) 15 February 1994 See 4 <sup>1</sup> ,7,8-trihydroxyisoflavone (relates to instant formula I)	41-43
X	Patent Abstracts of Japan, JP 6-040909 A (KOBE STEEL LTD) 15 February 1994 See 4 <sup>1</sup> ,7,8-trihydroxyisoflavone (relates to instant formula I)	41-43
X	Patent Abstracts of Japan, C-79, page 743, JP 2-124883 A (THE KITASATO INSTITUTE) 14 May 1990 See formula (relates to instant formulas I, IV and V)	41-44
X	Patent Abstracts of Japan, C-146, page 662, JP 1-226824 (OTA ISAN K K) 11 September 1989 See formula I (relates to instant formula I)	41-44
X	Derwent Abstract Accession No: 27437 A/15, Class B02, D16, JP 50-160483 (MICROBIOCHEMICAL RE) 25 December 1975 See formula I (relates to instant formula I)	41-44

## INTERNATIONAL SEARCH REPORT

International application No. PCT/AU 00/00103
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Derwent Abstract Accession No: 02698 X/02, Class B02, JP 50-101360 (MICROBIAL CHEM RES INST) 11 August 1975 See formulas I and II (relates to instant formula I)	41-44
X	Derwent Abstract Accession No: 56352 W/34, Class B02, D16, JP 50-0035393 (MICROBIOCH RES FOUN) 4 April 1975 See formulas I to III (relates to instant formula IV)	41-44
Y	G P Ellis, "Chromenes, Chromanones and Chromones", published 1977 by John Wiley & Sons (New York) pages 256-260	16-26

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/AU 00/00103

**Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
  
  
2.  Claims Nos.: 1-11, 16-24, 27-36, 41-43 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
The claims cannot be fully searched on economic grounds. An STN search with restricted substituents on positions 7, 8, 31 and 41 of isoflavone skeleton yielded one hundred and ninety-one flags for formula I of claim 41, two for formula-III, twenty-eight for formula IV and fifty-two for formula V. The flags are revealed by compound name and only three were interrogated to yield actual citations.
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

**Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
  
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Pr test**

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International application No.  
**PCT/AU 00/00103**

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
AU	80655/87 B	DD	275048	DK	5756/87	EP	267155
		FI	874804	HU	48611	JP	63130589
		NO	874489	NZ	222411	PT	86055
		US	4814346	ZA	8708245		
JP	10-059956	NONE					
JP	6-321752	NONE					
JP	6-86682	NONE					
JP	6-040876	NONE					
JP	6-040909	NONE					
JP	2-124883	NONE					
JP	1-226824	NONE					
JP	50-160483	NONE					
JP	50-101360	NONE					
JP	50-035393	CA	1038317	US	3973608	US	3974184

END OF ANNEX